



ADVANCES IN HETEROCYCLIC CHEMISTRY

Volume 28

A. R. Katritzky &
A. J. Boulton

Advances in

**Heterocyclic
Chemistry**

Volume 28

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Advances in

HETEROCYCLIC CHEMISTRY

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Preface

Volume 28 consists of five contributions that cover a diverse range of topics. A complete organic chemistry based on fluorocarbon rather than hydrocarbon skeletons can be conceived: Several general accounts of fluorocarbon chemistry have previously appeared; now, Chambers and Sargent have, for the first time, specifically devoted a review to heterocyclic aspects of this chemistry in the "Polyfluoroheteroaromatic Compounds." The 1,2- and 2,1-benzothiazines were virtually unknown 25 years ago. Today the position is very different, and Lombardino and Kuhla have given us a timely compilation of their chemistry. Isatoic anhydride is an important industrial chemical from which a very large number of different heterocyclic compounds can easily be derived. The uses of isatoic anhydrides in heterocyclic synthesis are now reviewed by Kappe and Stadlbauer. Numerous previous descriptions of benzyne chemistry have given scant regard to heterocyclic aspects. For this reason, Bryce and Vernon have discussed the reactions of benzyne with heterocyclic compounds. The role of carbenes and nitrenes in heterocyclic chemistry is a very large one. In this volume Wentrup presents the first part of a comprehensive account which is concerned with intramolecular reactions.

A. R. KATRITZKY
A. J. BOULTON

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Polyfluoroheteroaromatic Compounds

R. D. CHAMBERS AND C. R. SARGENT*

Department of Chemistry, University of Durham, Durham City, England

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I. Introduction

In principle, a totally synthetic organic chemistry is possible¹⁻³ based on fluorocarbon rather than hydrocarbon skeletons, together with associated functional groups. Within this chemistry is the potentially vast field of

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¹ See, e.g., Chambers² and Hudlicky,³ and many publications referred to there.

² R. D. Chambers, "Fluorine in Organic Chemistry." Wiley (Interscience), New York, 1973.

³ M. Hudlicky, "Chemistry of Organic Fluorine Compounds." Ellis-Horwood, Chichester, 1976.

heterocyclic compounds, and in this chapter we will be concerned specifically with heteroaromatic derivatives, which have also been included in discussions by others.⁴⁻⁷ Many useful developments arise from studies of these remarkable fluorine-containing compounds, including the following: (a) *new effects*—new compounds and materials arise with often quite novel properties and effects—and (b) *new chemistry*—since functional groups are placed in entirely different electronic environments in fluorocarbon as compared with the corresponding hydrocarbon derivatives, we have a chemistry that is mechanistically novel, including reactions that are often complementary to those with which we are most familiar.

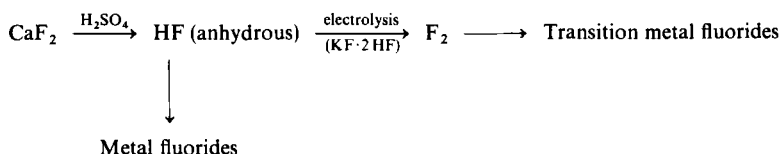
These comments could also be made about polychloro or polybromo derivatives, which are relatively neglected areas; but there is a unique relationship between fluorocarbon and corresponding hydrocarbon systems. This is due in part to similar volatilities of the systems, and contrasts with polychloro or polybromo derivatives, but the relationship is made even more striking by the availability of ¹⁹F-NMR spectroscopy as a powerful structural probe.

II. Synthesis

This part of the discussion can be divided into two sections, depending on whether fluorine is introduced into the preformed heterocycle or whether the heterocyclic system is formed by cyclization involving an already fluorinated compound.

A. INTRODUCTION OF FLUORINE INTO HETEROCYCLIC SYSTEMS

Fluorspar is the primary source of fluorine, but so far no useful process has been developed to use this directly for the purpose of forming carbon-fluorine bonds. Instead, the fluorspar may be converted to anhydrous hydrogen fluoride, elemental fluorine, and a range of fluorides or special reagents



⁴ G. G. Yakobson, T. D. Petrova, and L. S. Kобрina, *Fluorine Chem. Rev.* **7**, 115 (1974).

⁵ "Gmelin Handbuch der Anorganischen Chemie, Perfluorohalogen-organoVerbindungen der Hauptgruppenelemente," Parts 1-6. Springer-Verlag, Berlin and New York, 1973-1978.

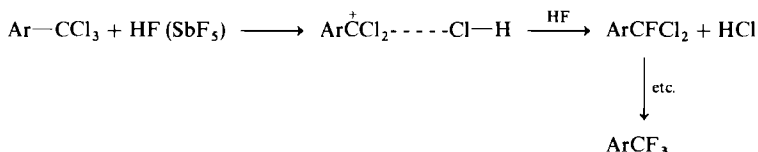
⁶ R. E. Banks and M. G. Barlow, eds., "Fluorocarbon and Related Chemistry," Vols. 1-3. Chemical Society, London, 1971, 1974, 1976.

⁷ M. M. Boudakian, in "Pyridine and Its Derivatives" (R. A. Abramovich, ed.), Vol. 14 Suppl., Pt. 2, p. 407. Wiley, New York, 1974.

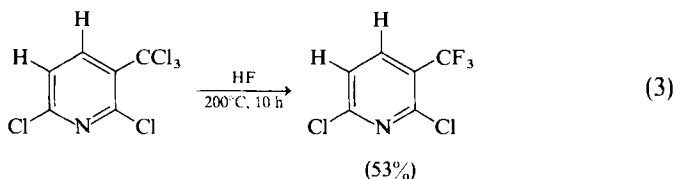
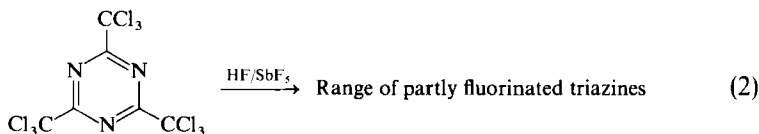
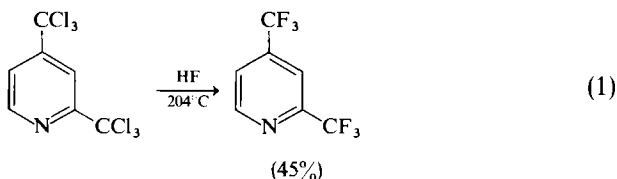
for the purpose of fluorination. Clearly from an economic viewpoint, anhydrous hydrogen fluoride (AHF) is the reagent of choice, but other reagents are frequently easier to handle on a laboratory scale.

1. Electrophilic Halogen Exchange

The well-established process^{8a} of using hydrogen fluoride, usually with antimony pentafluoride as catalyst, for converting a trichloromethyl group



attached to an aromatic ring to trifluoromethyl may be applied to heteroaromatic systems (Eqs. 1-3).^{8b-10} This process probably involves acid-induced ionization of the carbon-chlorine bond, the addition of antimony pentafluoride effectively providing a super acid. Consequently, it is understandable that trichloromethyl attached to, for example, a pyridine system will be less reactive in this type of exchange than when attached to phenyl.



Various metal fluorides have been used to form trifluoromethyl groups in processes of uncertain mechanism probably involving assistance to ionization

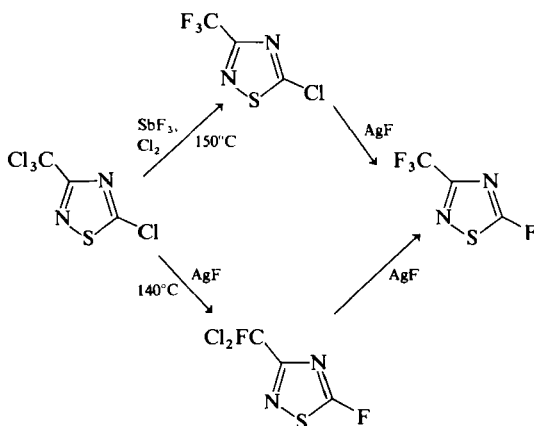
^{8a} A. K. Barbour, L. J. Belf, and M. W. Buxton, *Adv. Fluorine Chem.* **3**, 181 (1963).

^{8b} E. T. McBee, H. B. Hass, and E. M. Hodnett, *Ind. Eng. Chem.* **39**, 389 (1947).

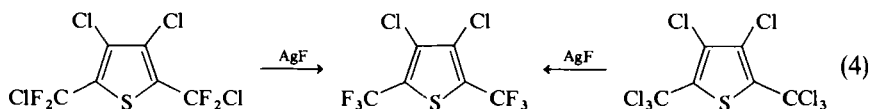
⁹ E. T. McBee, O. R. Pierce, and R. O. Bott, *Ind. Eng. Chem.* **39**, 391 (1947).

¹⁰ F. Mutterer and C. D. Weis, *Helv. Chim. Acta* **59**, 229 (1976).

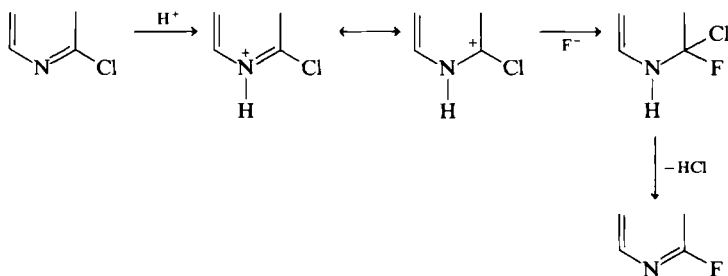
[e.g., see Scheme 1¹¹ and Eq. (4)¹²]; some of these procedures are rather drastic and therefore do not constitute realistic preparative procedures.



SCHEME 1



In certain cases, hydrogen fluoride may be used to exchange chlorine for fluorine attached directly to ring positions adjacent to ring nitrogen (Eqs. 5¹³ and 6^{14,15}). Here, it is tempting to attribute the reactivity to initial protonation of nitrogen (Scheme 2).



SCHEME 2

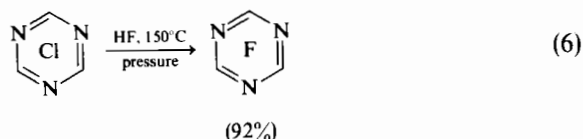
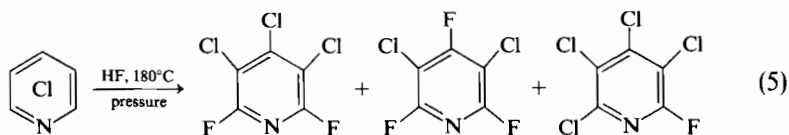
¹¹ H. Schroeder, R. Ratz, W. Schnabel, H. Ulrich, E. Kober, and C. Grundmann, *J. Org. Chem.* **27**, 2589 (1962).

¹² H. Ulrich, E. Kober, R. Ratz, H. Schroeder, and C. Grundmann, *J. Org. Chem.* **27**, 2593 (1962).

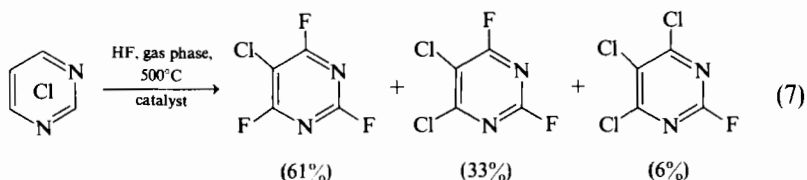
¹³ S. C. Carson and R. D. Howard, British Patent 1,272,475 (1972) [*CA* **77**, 126439 (1972)].

¹⁴ E. Kysela, E. Klauke, and H. Schwarz, German Patent 2,729,762 (1979) [*CA* **90**, 168649 (1979)].

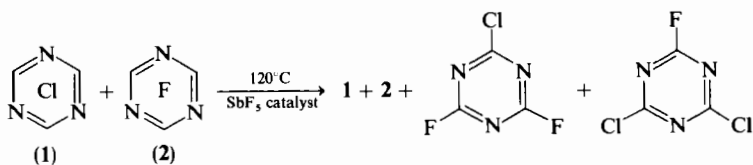
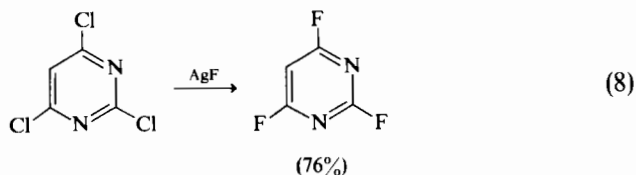
¹⁵ G. Seifert and S. Staebli, German Patent 2,814,450 (1978) [*CA* **90**, 23123 (1979)].



Vapor-phase fluorination using hydrogen fluoride and, for example, a chromium or aluminum oxide/fluoride catalyst (i.e., the procedures used for manufacture of fluorochloroalkanes¹⁶) has also been applied (Eq. 7).¹⁷



Metal fluorides have been used to exchange chlorine for fluorine at various ring positions^{18,19} (e.g., Eq. 8)¹⁸; and an interesting exchange of halogen between *sym*-trichlorotriazine (1) and *sym*-trifluorotriazine (2) has been promoted by antimony pentafluoride.²⁰



¹⁶ A. K. Barbour, in "Organofluorine Chemicals and Their Industrial Applications" (R.E. Banks, ed.), Chapter 2. Ellis Horwood, Chichester, 1979.

¹⁷ H. U. Alles, E. Klauke, and H. S. Bien, German Patent, 1,931,640 (1970) [CA 74, 76439 (1971)].

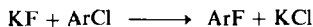
¹⁸ H. Schroeder, E. Kober, H. Ulrich, R. Ratz, H. Agahigian, and C. Grundmann, J. Org. Chem. 27, 2580 (1962).

¹⁹ E. Kober, H. Schroeder, R. F. W. Ratz, H. Ulrich, and C. Grundmann, J. Org. Chem. 27, 2577 (1962).

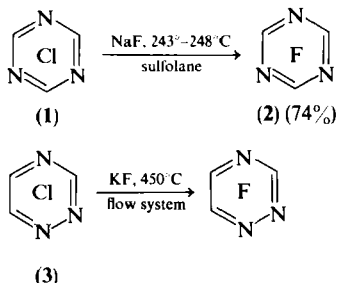
²⁰ E. Kysela, E. Klauke, and A. Dorlars, German Patent 2,729,769 (1979) [CA 90, 168649 (1979)].

2. Nucleophilic Halogen Exchange

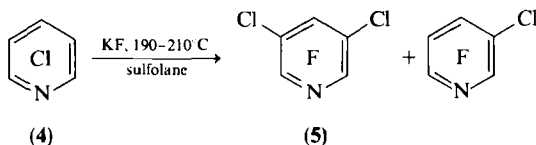
One of the most practical laboratory routes to highly fluorinated hetero-aromatic compounds involves the use of potassium or other alkali metal fluorides in nucleophilic displacement of chlorine by fluorine, from aromatic systems activated toward nucleophilic attack. Reactivity of the alkali metal



fluorides decreases in the series $\text{CsF} > \text{KF} \gg \text{NaF}$ (i.e., with increasing lattice energy), and because the reactivity of fluoride as a nucleophile decreases sharply on solvation, dipolar aprotic solvents are often used. The very reactive trichloro-1,3,5-triazine (**1**) is converted to the trifluoro derivative (**2**) with sodium fluoride²¹ and the trichloro-1,2,4-triazine (**3**) apparently requires only short contact in the vapor phase for successful fluorination.²²



Reaction of pentachloropyridine (**4**) with potassium fluoride in sulfolane leads mainly to 2,4,6-trifluoropyridine (**5**)²³; milder reaction conditions may be employed using potassium fluoride and 18-crown-6 polyether in acetonitrile but fluorination proceeds only to **5**.^{24,25} It is claimed²⁶ that even so-



²¹ C. W. Tullock and D. D. Coffman, *J. Org. Chem.* **25**, 2016 (1960).

²² M. G. Barlow, R. N. Haszeldine, and D. J. Simpkin, *J. C. S. Chem. Commun.*, 658 (1979).

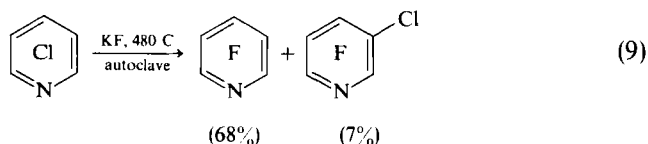
²³ R. D. Chambers, J. Hutchinson, and W. K. R. Musgrave, *Proc. Chem. Soc., London*, 83 (1964); *J. Chem. Soc.*, 3573 (1964).

²⁴ N. E. Akhmetova, V. M. Vlasov, and G. G. Yakobson, *Bull. Acad. Sci. USSR, Div. Chem. Sci.* **27**, 823 (1978).

²⁵ R. D. Chambers and D. Pearce, unpublished observations.

²⁶ A. Nicholson and R. B. Paton, British Patent 1,340,421 (1973) [*CA* **80**, 95756 (1974)].

dium fluoride may be used effectively for the conversion of **4** to **5**. The feature that limits the extent of fluorination under these conditions is, essentially, the thermal stability of the solvents used. This problem has been circumvented by two approaches: (a) using a melt of potassium fluoride–potassium chloride at temperatures in the region of 750°C²⁷ and, more successfully, (b) employing autoclaves at high temperatures for reactions in the absence of a solvent^{23,28} (Eq. 9).



A general process has now evolved for the synthesis of highly fluorinated azabenzenoid compounds involving (a) synthesis of the perchloro compound, by further chlorination of partly chlorinated compounds with phosphorus pentachloride and (b) subsequent reaction of the perchloro compound with potassium or even sodium fluoride. Some examples are shown in Table I.^{29–44}

²⁷ H. C. Fielding, L. P. Gallimore, H. L. Roberts, and B. Tittle, *J. Chem. Soc. C*, 2142 (1966).

²⁸ R. E. Banks, R. N. Haszeldine, J. V. Latham, and I. M. Young, *Chem. Ind., (London)*, 835 (1964); *J. Chem. Soc.*, 594 (1965).

²⁹ R. D. Bowden, M. B. Green, and A. Nicolson, British Patent 1,306,596 (1973) [*CA* **78**, 136089 (1973)].

³⁰ R. E. Banks, R. N. Haszeldine, K. H. Legge, and F. E. Rickett, *J.C.S. Perkin I*, 2367 (1974).

³¹ R. D. Chambers, J. A. H. MacBride, and W. K. R. Musgrave, *J. Chem. Soc. C*, 2116 (1968).

³² R. D. Chambers, J. A. H. MacBride, and W. K. R. Musgrave, *Chem. Ind., (London)*, 1721 (1966).

³³ R. E. Banks, D. S. Field, and R. N. Haszeldine, *J. Chem. Soc. C*, 1822 (1967).

³⁴ Farbenfabriken Bayer A. G., French Patent 1,546,305 (1968) [*CA* **72**, 90492 (1970)].

³⁵ R. E. Banks, D. S. Field, and R. N. Haszeldine, *J. Chem. Soc. C*, 1280 (1970).

³⁶ C. G. Allison, R. D. Chambers, J. A. H. MacBride, and W. K. R. Musgrave, *J. Chem. Soc. C*, 1023 (1970).

³⁷ D. W. Grisley, E. W. Gluesenkamp, and S. A. Heininger, *J. Org. Chem.* **23**, 1802 (1958).

³⁸ J. K. Chakrabarti, A. F. Cockerill, G. L. O. Davies, T. M. Hotten, D. M. Rackham, and D. E. Tupper, *J.C.S. Perkin II*, 861 (1974).

³⁹ R. D. Chambers, M. Hole, B. Iddon, W. K. R. Musgrave, and R. A. Storey, *J. Chem. Soc. C*, 2328 (1966).

⁴⁰ D. M. W. Van den Ham, *J. Fluorine Chem.* **5**, 537 (1975).

⁴¹ R. D. Chambers, J. A. H. MacBride, W. K. R. Musgrave, and I. S. Reilly, *Tetrahedron Lett.*, 57 (1970).

⁴² R. D. Chambers, J. A. H. MacBride, and W. K. R. Musgrave, *Chem. Commun.*, 739 (1970).

⁴³ C. G. Allison, R. D. Chambers, J. A. H. MacBride, and W. K. R. Musgrave, *Tetrahedron Lett.*, 1979 (1970).

⁴⁴ C. G. Allison, R. D. Chambers, J. A. H. MacBride, and W. K. R. Musgrave, *J. Fluorine Chem.* **1**, 59 (1971–1972).

TABLE I
DISPLACEMENT OF CHLORINE BY FLUORINE USING POTASSIUM OR SODIUM FLUORIDE


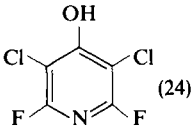
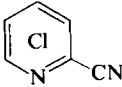
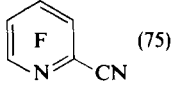

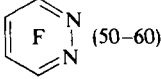

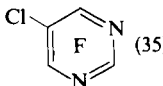
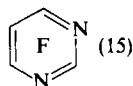
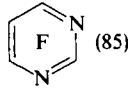

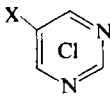
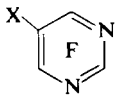

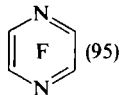

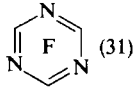
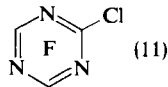
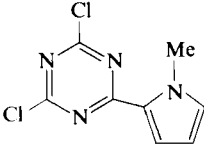
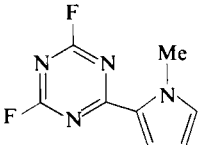
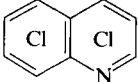
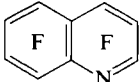
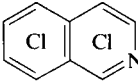

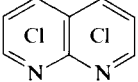

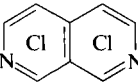
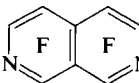
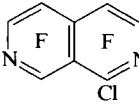
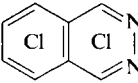

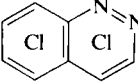

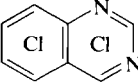
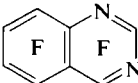
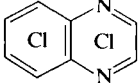
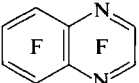
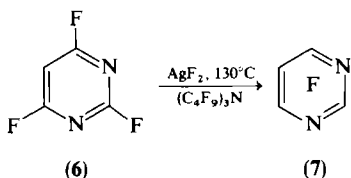
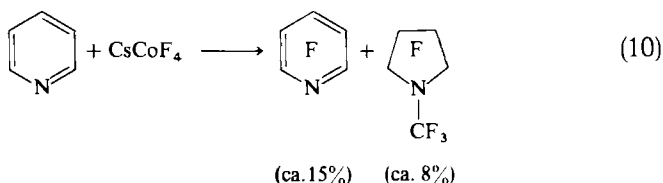
Compound	Conditions (temp., °C)	Products (% yields)	References
	KF, KOAc (210) Sulfolane, ethylene glycol	 (24)	29
	KF (380)	 (75)	30
	KF (305–310)	 (50–60)	31
	KF (325–345)	 (35)  (15)	32
	KF (480)	 (85)	33
	NaF (300)	 (93)	34
 X = NO ₂ ; CN	KF (250)	 + partly fluorinated compounds	35
	KF (310–320)	 (95)	36
	KSO ₂ F (120–150)	 (31)  (11)	37

TABLE I (Continued)

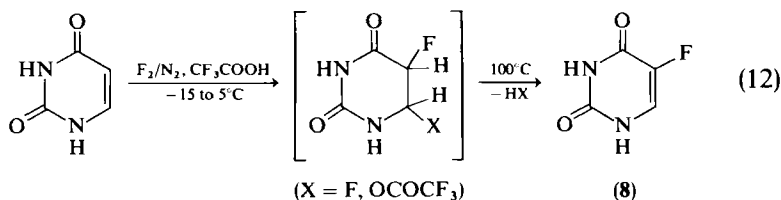
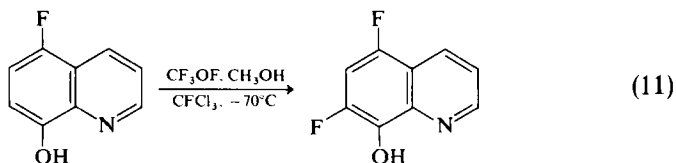
Compound	Conditions (temp., °C)	Products (% yields)	References
	KF, boiling isobutyl methyl ketone	 (73)	38
	KF (470)	 (73)	39
	KF (420)	 (92)	39
	KF, sulfolane (200)	 (33)	40
+ partly fluorinated compounds			
	KF, CsF (200)	 (33)	40
		 (35)	
	KF (290)	 (60)	41
	KF (290)		42
	KF (350)		43
	KF (380)	 (50)	44

3. Substitution of Hydrogen by Fluorine

In principle, this would be the preferred route, but in practice no generally successful procedure is available for the synthesis of highly fluorinated compounds directly by this approach. It has been reported that pentafluoropyridine may be obtained in approximately 15% yield by fluorinating pyridine over cesium tetrafluorocobaltate (Eq. 10).⁴⁵ But it appears that



yields diminish with increasing scale. Silver difluoride has been used in the final stage of an earlier synthesis of tetrafluoropyrimidine (7) from trifluoropyrimidine (6),¹⁸ which is now superseded by halogen exchange (see preceding section). Various partly fluorinated compounds may be obtained by direct synthesis using selective fluorinating agents such as trifluoromethyl



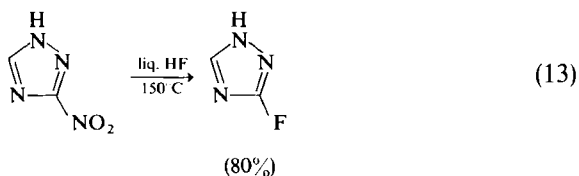
⁴⁵ A. J. Edwards, R. G. Plevey, and J. C. Tatlow, British Patent 1,392,571 (1975); R. G. Plevey, private communication.

hypofluorite^{46,47} or even fluorine,^{48,49} as shown (Eqs. 11 and 12),^{46,48} and compounds like 5-fluorouracil (**8**) are of tremendous clinical importance as anticancer drugs. However, the extent of fluorination by these procedures is limited. Indeed, the objective in fluorinating biologically significant molecules is to achieve very limited fluorination.

4. Substitution of Other Groups

Various partly fluorinated pyridines can be synthesized by diazotization of the amino derivatives in aqueous hydrofluoric acid,⁵⁰ or by using anhydrous hydrogen fluoride followed by thermal decomposition of the diazonium fluoride.^{51,52} There are also many examples of the application of the classical Balz-Schiemann reaction to heteroaromatic systems,^{53,54} and the interesting photolysis of diazonium tetrafluoroborates has given fluoroimidazole derivatives^{55,56} and fluorazoles.⁵⁷

The replacement of a nitro group by fluorine in some triazoles has been achieved using anhydrous hydrogen fluoride (Eq. 13)⁵⁸ and, in 2- and 4-nitropyridines and 2-nitrothiazole, by using potassium fluoride in aprotic solvents (Eq. 14).⁵⁹



⁴⁶ H. Gershon, M. W. McNeil, R. Parmegiani, and P. K. Godfrey, *J. Med. Chem.* **15**, 987 (1972).

⁴⁷ D. H. R. Barton, R. H. Hesse, H. T. Toh, and M. M. Pechet, *J. Org. Chem.* **37**, 329 (1972).

⁴⁸ S. Misaki and Y. Furutaka, Japan Kokai 76/149,287 (1976) [*CA* **87**, 135378 (1977)].

⁴⁹ T. Kanai, M. Ichino, and T. Nakamura, Japan Kokai 74/76,882 (1974) [*CA* **82**, 16863 (1975)].

⁵⁰ T. Talik and Z. Talik, *Rocz. Chem.* **47**, 441 (1973) [*CA* **79**, 18534 (1973)].

⁵¹ M. M. Boudakian, U.S. Patent 3,703,521 (1972) [*CA* **78**, 29,635 (1973)].

⁵² M. M. Boudakian and S. J. Chiras, U.S. Patent 3,798,228 (1974) [*CA* **80**, 146,026 (1974)].

⁵³ J. L. Lyle and R. W. Taft, *J. Heterocycl. Chem.* **9**, 745 (1972).

⁵⁴ R. K. Smalley, in "The Chemistry of Heterocyclic Compounds" (G. Jones, ed.), Vol. 32, Chapter 3, Wiley (Interscience), New York, 1977.

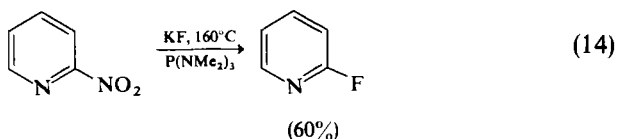
⁵⁵ K. L. Kirk and L. A. Cohen, *J. Am. Chem. Soc.* **95**, 4619 (1973).

⁵⁶ K. L. Kirk, W. Nagai, and L. A. Cohen, *J. Am. Chem. Soc.* **95**, 8389 (1973).

⁵⁷ F. Fabra, J. Vilarrasa, and J. Coll, *J. Heterocycl. Chem.* **15**, 1447 (1978).

⁵⁸ S. R. Naik, J. T. Witkowski, and R. K. Robins, *J. Org. Chem.* **38**, 4353 (1973).

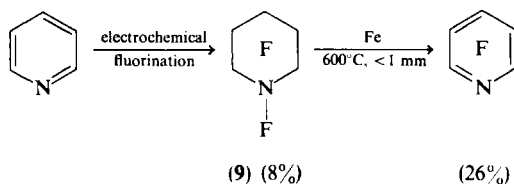
⁵⁹ G. Bartoli, A. Latrofa, F. Naso, and P. E. Todesco, *J.C.S. Perkin I*, 2671 (1972).



A number of fluorothiophenes have been prepared by the action of perchloryl fluoride on thienyllithium derivatives, which were obtained from the corresponding bromothiophenes by metal-bromine exchange with ethyllithium.⁶⁰

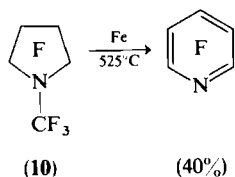
5. Saturation-Rearomatization

Procedures involving the formation of saturated fluorocarbons followed by defluorination (e.g., over iron) have been very successful in the synthesis of benzenoid compounds.¹ However, defluorination of perfluoropiperidine (**9**) is not a practical synthesis of pentafluoropyridine.⁶¹ An indirect process has been described recently for the preparation of pentafluoropyridine from



perfluoro-*N*-methylpyrrolidine (**10**) by passing it over hot iron.⁴⁵

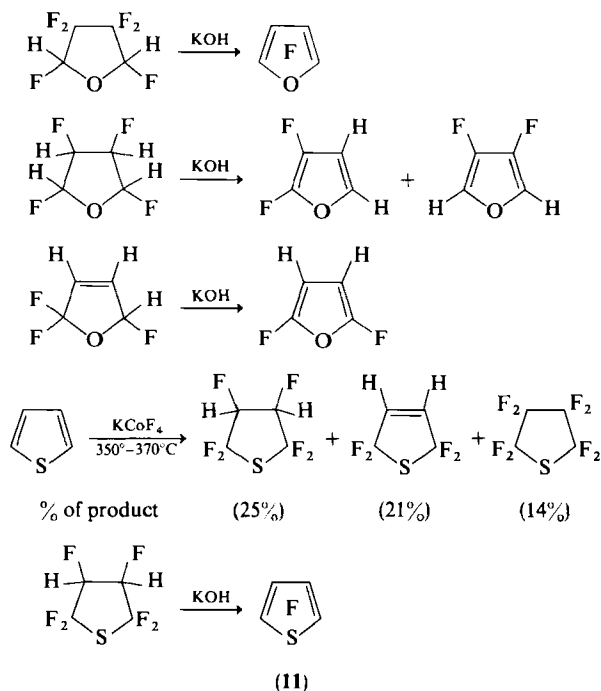
Since **10** and pentafluoropyridine are the principal products in the small-scale fluorination of pyridine over cesium tetrafluorocobaltate (Eq. 10), this constitutes an overall direct synthesis of pentafluoropyridine via a very interesting rearrangement.



⁶⁰ S. Gronowitz and U. Rosen, *Chem. Scr.* **1**, 33 (1971) [*CA* **75**, 20080 (1971)].

⁶¹ R. E. Banks, A. E. Ginsberg, and R. N. Haszeldine, *J. Chem. Soc.*, 1740 (1961).

Saturation–rearomatization procedures have provided useful routes to fluorinated furan and thiophene derivatives. A range of polyfluorofurans and polyfluorothiophenes is obtained by reaction of products obtained from the parent compounds with cobalt trifluoride,^{62,63} or the less reactive



SCHEME 3

KCoF₄,^{63,64} with potassium hydroxide^{65,66} (Scheme 3). Tetrafluorothiophene (11) has also been prepared by a route involving a final dechlorination step using zinc (Eq. 15)⁶⁷; and 2,5-difluorothiophene (13) by the unusual defluorination of 2,2,5,5-tetrafluoro-3-thiolene (12) over sodium fluoride.⁶⁸ Perfluorobenzofuran (15) can be prepared by reaction of benzofuran (14) with CsCoF₄, followed by defluorination with nickel.⁶⁹

⁶² J. Burdon, G. E. Chivers, E. F. Mooney, and J. C. Tatlow, *J. Chem. Soc. C*, 1739 (1969).

⁶³ J. Burdon, I. W. Parsons, and J. C. Tatlow, *J. Chem. Soc. C*, 346 (1971).

⁶⁴ J. Burdon, G. E. Chivers, and J. C. Tatlow, *J. Chem. Soc. C*, 2585 (1969).

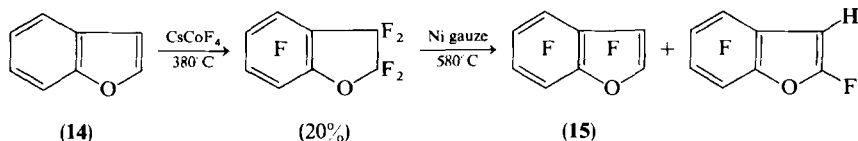
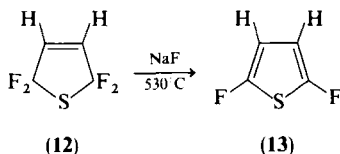
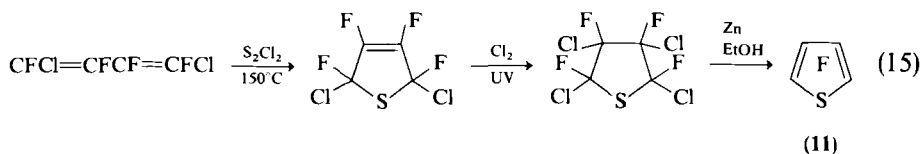
⁶⁵ J. Burdon, G. E. Chivers, and J. C. Tatlow, *J. Chem. Soc. C*, 2146 (1970).

⁶⁶ J. Burdon, J. G. Campbell, I. W. Parsons, and J. C. Tatlow, *J. Chem. Soc. C*, 352 (1971).

⁶⁷ E. M. Ilgenfritz and R. P. Ruh, U.S. Patent 2,932,651 (1960) [*CA* **54**, 18549 (1960)].

⁶⁸ J. Burdon and I. W. Parsons, *J. Fluorine Chem.* **13**, 159 (1979).

⁶⁹ J. Bailey, R. G. Plevy, and J. C. Tatlow, *Tetrahedron Lett.*, 869 (1975).



B. CYCLIZATIONS USING FLUORINATED PRECURSORS

1. Involving Fluorinated Benzene Derivatives

There is now a significant literature on the subject of cyclizations involving fluorinated benzene derivatives, and reference should be made to earlier reviews^{1-6,70} for more general aspects, since here we will only be concerned with processes that lead to aromatic heterocycles as opposed to heterocycles that are themselves not aromatic but are attached to aromatic rings.

a. Intramolecular Nucleophilic Aromatic Displacement of Fluoride.

One of the most direct approaches to the synthesis of heteroaromatic compounds involves nucleophiles that are potentially difunctional. The generalized system (16) has a site acidified by the nearby heteroatom, but on substitution the heteroatom may become a further nucleophilic site and available for ring closure. Sometimes these processes can both be carried out in one-step procedures, or the intermediate (17) may be isolated before cyclization (Scheme 4). Various benzofuran derivatives have been obtained using this procedure⁷¹⁻⁷⁵ (Eqs. 16⁷¹ and 17,⁷² Scheme 5⁷³), and the use of

⁷⁰ S. C. Cohen and A. G. Massey, *Adv. Fluorine Chem.* **6**, 83 (1970).

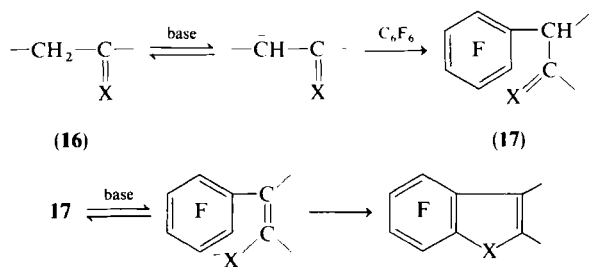
⁷¹ G. G. Yakobson, T. D. Petrova, L. I. Kann, T. I. Savchenko, A. K. Petrov, and N. N. Vorozhtsov, *Dokl. Akad. Nauk SSSR* **158**, 926 (1964) [*CA* **62**, 2755 (1965)].

⁷² Y. Inukai, T. Sonoda, and H. Kobayashi, *Bull. Chem. Soc. Jpn.* **52**, 2657 (1979).

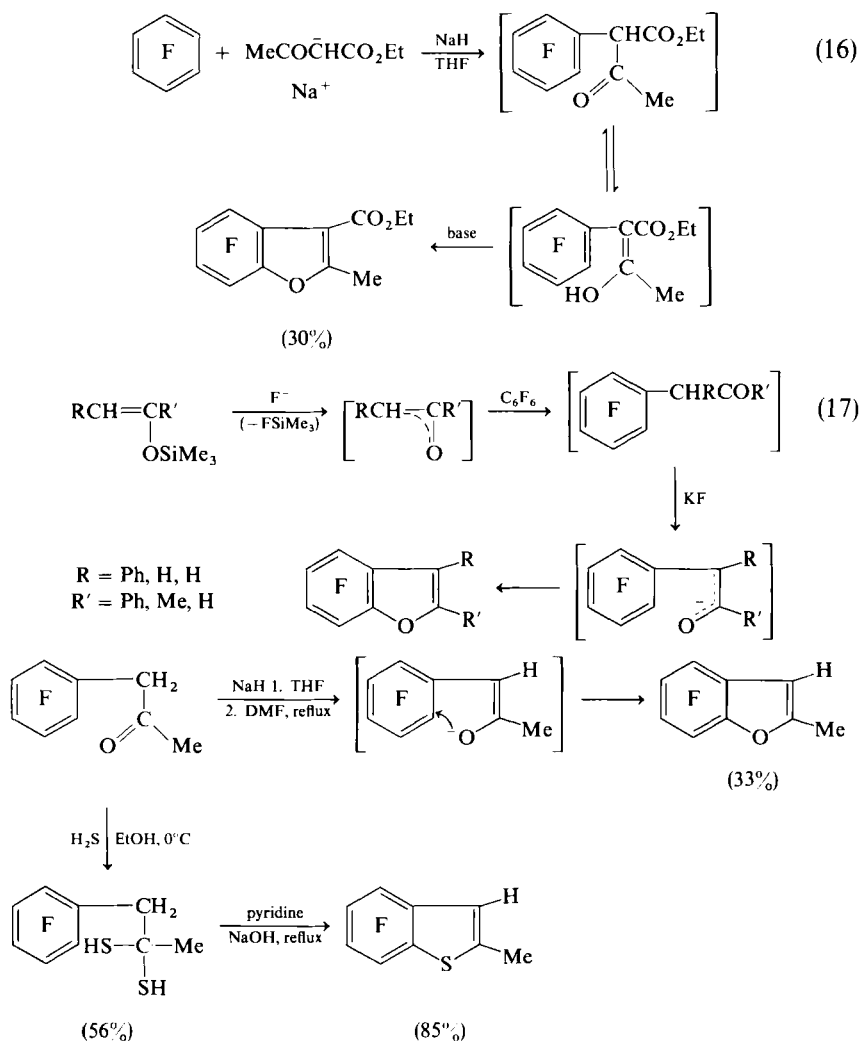
⁷³ G. M. Brooke, *Tetrahedron Lett.*, 2029, 4049 (1968).

⁷⁴ G. M. Brooke, W. K. R. Musgrave, and T. R. Thomas, *J. Chem. Soc. C*, 3596 (1971).

⁷⁵ T. D. Petrova, L. I. Kann, V. A. Barkhash, and G. G. Yakobson, *Khim. Geterotsikl. Soedin.*, 778 (1969) [*CA* **72**, 111190 (1970)].

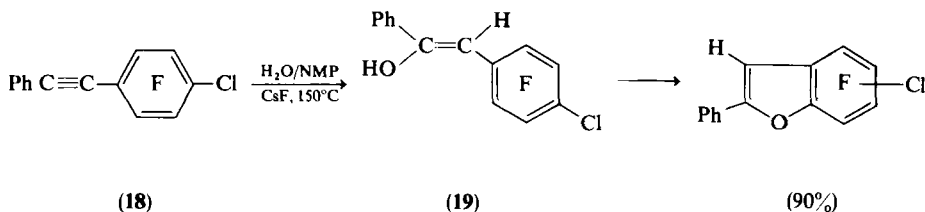


SCHEME 4

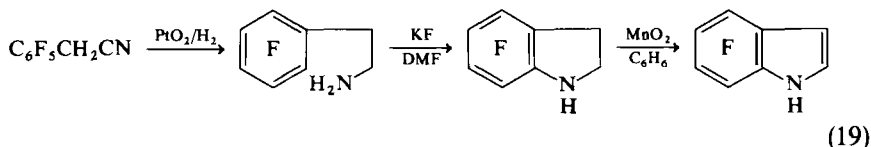
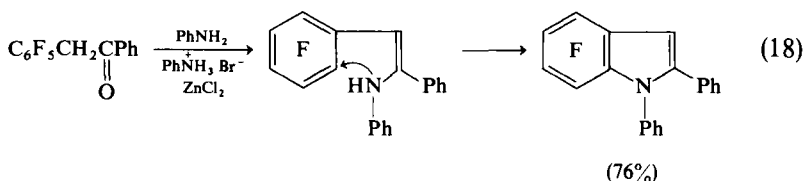


SCHEME 5

the trimethylsilyl group (Eq. 17) is an interesting variation for the cyclization step. Also, the precursor for cyclization (19) has been generated by addition of water to the acetylene (18) in a reaction catalyzed by cesium fluoride.⁷⁶



Corresponding reactions involving cyclization through sulfur^{73,77} (Scheme 5⁷³) have also been described. Indole derivatives have been obtained^{78–85} by cyclization through nitrogen, but in these cases the precursors are often made from appropriate carbonyl compounds (Eq. 18),⁷⁹ where carbonyl has served the purpose of facilitating carbanion formation for the first displacement of fluoride in Scheme 4. The nitrile function is also effective for this purpose^{80,81} (Eq. 19).



⁷⁶ M. R. Wiles and A. G. Massey, *J. Organometal. Chem.* **47**, 423 (1973).

⁷⁷ M. D. Castle, R. G. Plevy, and J. C. Tatlow, *J. Chem. Soc. C*, 1225 (1968).

⁷⁸ V. P. Petrov and V. A. Barkhash, *J. Gen. Chem. USSR (Engl. Transl.)* **39**, 1583 (1969).

⁷⁹ G. M. Brooke, W. K. R. Musgrave, R. J. D. Rutherford, and T. W. Smith, *Tetrahedron* **27**, 5653 (1971).

⁸⁰ R. Filler, S. M. Woods, and A. F. Freudenthal, *J. Org. Chem.* **38**, 811 (1973).

⁸¹ T. D. Petrova, T. I. Savchenko, O. S. Kukovinets, and G. G. Yakobson, *Izv. Sib. Otd. Akad. Nauk SSSR, Ser. Khim. Nauk*, 117 (1974) [*CA* **81**, 25488 (1974)].

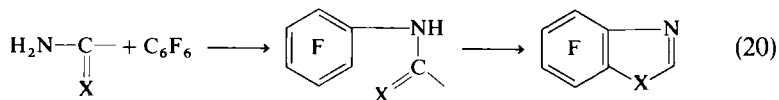
⁸² V. P. Petrov, V. A. Barkhash, G. S. Shchegoleva, T. D. Petrova, T. I. Savchenko, and G. G. Yakobson, *Dokl. Akad. Nauk SSSR* **178**, 864 (1968) [*CA* **69**, 35851 (1968)].

⁸³ V. P. Petrov and V. A. Barkhash, *Khim. Geterotsikl. Soedin.*, 622 (1970) [*CA* **73**, 98720 (1970)].

⁸⁴ T. D. Petrova, T. I. Savchenko, T. F. Ardyukova, and G. G. Yakobson, *Izv. Sib. Otd. Akad. Nauk SSSR, Ser. Khim. Nauk*, 119 (1970) [*CA* **74**, 53393 (1971)].

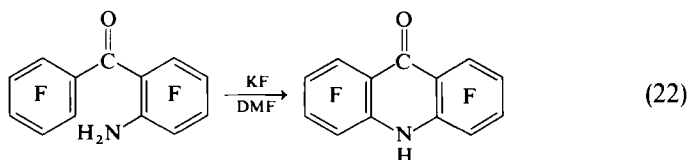
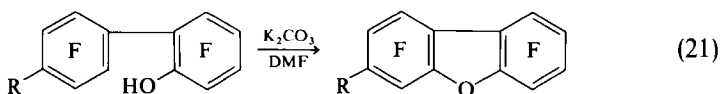
⁸⁵ V. P. Petrov and V. A. Barkhash, *Khim. Geterotsikl. Soedin.*, 381, 385 (1970) [*CA* **73**, 25229, 98721 (1970)].

The amino function may be used in conjunction with other heteroatoms (Eq. 20) to effect cyclization in a manner analogous to that outlined for carbanions in Scheme 4. In this way heterocycles containing two nitrogen

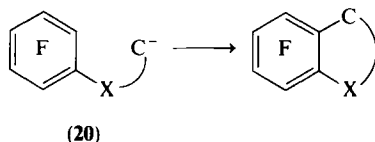


atoms⁸⁶ or nitrogen together with oxygen^{72,87,88} or sulfur^{56,89} have been obtained.

Intramolecular nucleophilic substitution of fluoride by heteroatoms can also lead to tricyclic systems such as dibenzofuran⁹⁰ and acridinone⁹¹ derivatives (Eqs. 21 and 22).



Ring closure could also be effected via displacement of fluoride ion by a carbanion (20) already having formed a link with the appropriate hetero-



atom. So far, species like **20** have been generated *in situ* by the interesting addition of sulfur (Eq. 23)⁹² or nitrogen (Eq. 24)⁹³ nucleophiles to acetylenedicarboxylic ester. Quite reasonably, the success of these reactions has been

⁸⁶ Y. Inukai, Y. Oono, T. Sonoda, and H. Kobayashi, *Bull. Chem. Soc. Jpn.* **52**, 516 (1979).

⁸⁷ G. S. Shchegoleva and V. A. Barkhash, *Izv. Sib. Otd. Akad. Nauk SSSR, Ser. Khim. Nauk*, 123 (1971) [*CA* **77**, 48316 (1972)].

⁸⁸ G. S. Shchegoleva, M. I. Kollegova, and V. A. Barkhash, *Izv. Sib. Otd. Akad. Nauk SSSR, Ser. Khim. Nauk*, 126 (1971) [*CA* **77**, 101494 (1972)].

⁸⁹ F. C. Herkes, *J. Fluorine Chem.* **12**, 1 (1978).

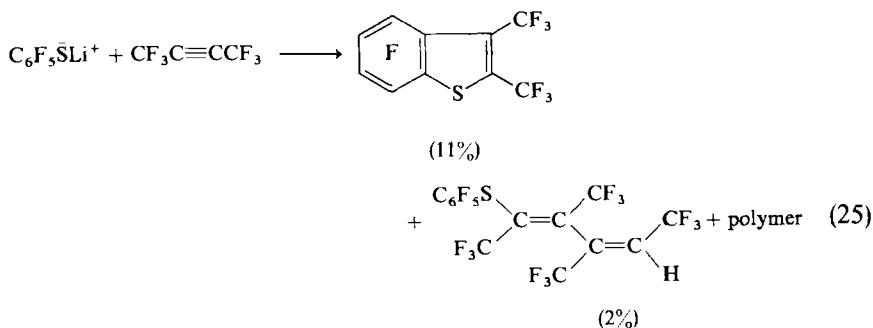
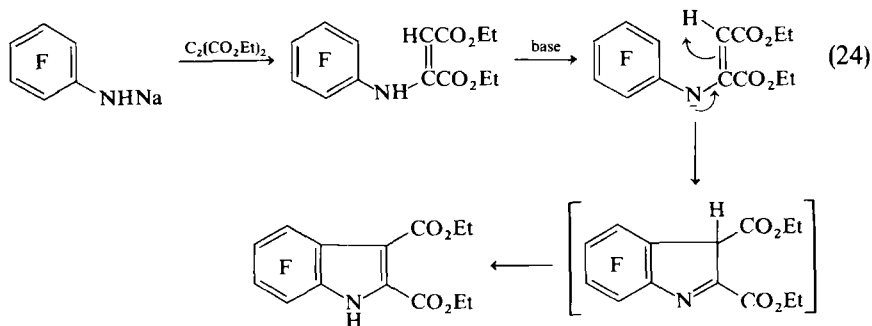
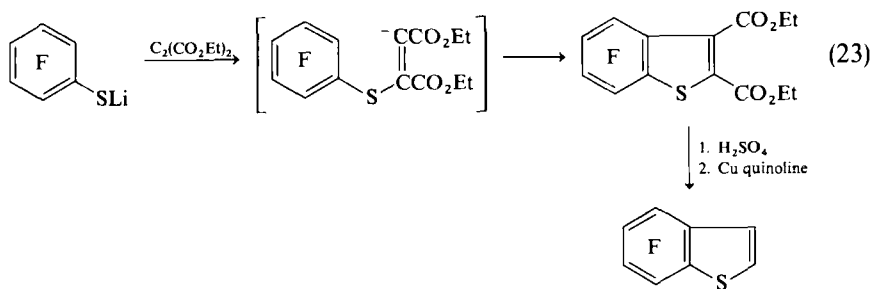
⁹⁰ P. J. N. Brown, R. Stephens, and J. C. Tatlow, *Tetrahedron* **23**, 4041 (1967).

⁹¹ D. M. Owen, A. E. Pedler, and J. C. Tatlow, *J.C.S. Perkin I*, 1380 (1975).

⁹² G. M. Brooke and M. A. Quasem, *J. Chem. Soc. C*, 865 (1967).

⁹³ G. M. Brooke and R. J. D. Rutherford, *J. Chem. Soc. C*, 1189 (1967).

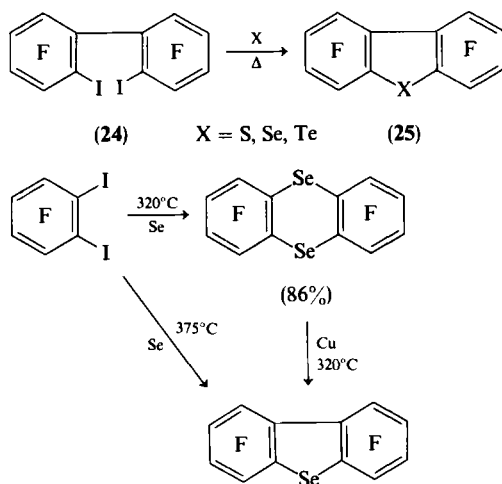
attributed to syn-addition to acetylenedicarboxylic ester, therefore allowing easy ring closure of the intermediate carbanion corresponding to **20**. Consequently, the lower yields obtained in the corresponding reactions using hexafluoro-2-butyne (Eq. 25)⁹⁴ may be ascribed to a competing anti-addition, since syn-addition in this case requires placing bulky trifluoromethyl groups in closer proximity.



An extension of the method⁹⁵ involves addition to tetrafluorobenzynes, generated *in situ* from pentafluorophenyllithium (Eq. 26).

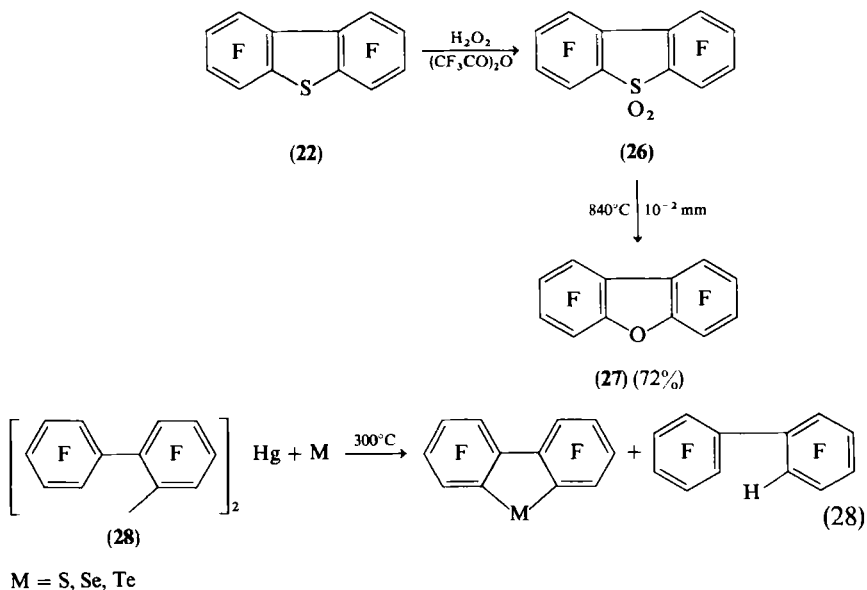
⁹⁴ G. M. Brooke and M. A. Quasem, *J.C.S. Perkin I*, 429 (1973).

⁹⁵ R. D. Chambers and D. J. Spring, *Tetrahedron Lett.*, 2481 (1969).



SCHEME 6

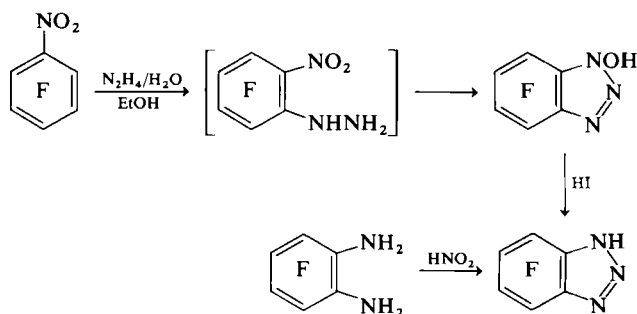
pyrolytic elimination of SO from the dioxide (26).¹⁰⁰ Related to these interconversions but not strictly involving difunctional derivatives, is the conversion of the mercurial **28** to various heterocycles (Eq. 28).¹⁰¹



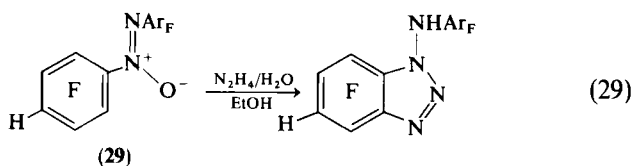
¹⁰⁰ R. D. Chambers, J. A. Cunningham, and D. J. Spring, *J. Chem. Soc. C*, 1560 (1968).

¹⁰¹ C. M. Woodward, G. Hughes, and A. G. Massey, *J. Organomet. Chem.* **112**, 9 (1976).

It is uncommon for substitution in a pentafluorobenzene derivative C_6F_5X to occur predominantly at a position ortho to the functional group X, but when nitro or *N*-oxide groups are present, attack by ammonia or hydrazine seems to be governed by hydrogen bonding between group X and the incoming nucleophile. The formation of cyclic compounds in reactions of nitropentafluorobenzene and **29** with hydrazine hydrate may be understood as formation of an intermediate hydrazino compound which reacts further (Scheme 7 and Eq. 29).¹⁰² A directing influence of carbonyl in pentafluoroacetophenone to the ortho position, for attack by amines, may also be



SCHEME 7



attributed to the effects of hydrogen bonding, and these substitution products form cyclized compounds by reaction with acid (Scheme 8¹⁰³). This type of cyclization, via intramolecular electrophilic aromatic substitution, has similarly been utilized in the preparation of acridine¹⁰⁴⁻¹⁰⁷ and phenanthridine¹⁰⁸ derivatives.

¹⁰² J. M. Birchall, R. N. Haszeldine, and J. E. G. Kemp, *J. Chem. Soc. C*, 1519 (1970).

¹⁰³ T. N. Gerasimova, L. L. Gelumbovskaya, I. I. Baturina, and E. P. Fokin, *Izv. Sib. Otd. Akad. Nauk SSSR, Ser. Khim. Nauk*, 88 (1973) [*CA* **79**, 53161 (1973)].

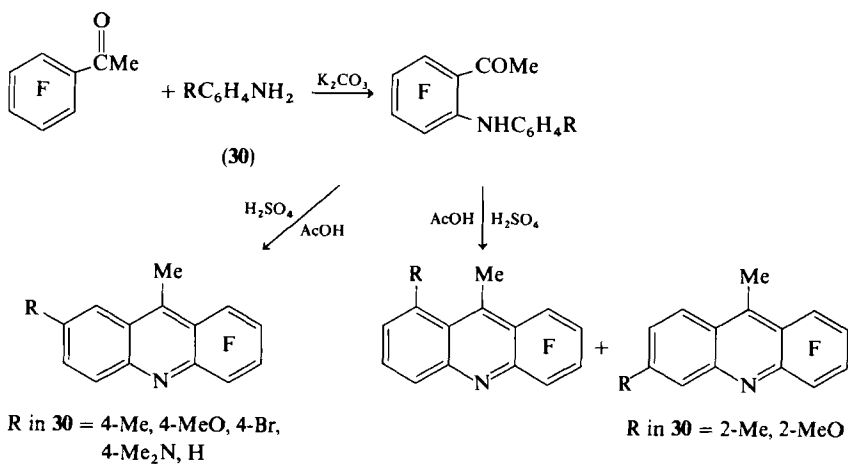
¹⁰⁴ N. A. Orlova, L. L. Dmitrieva, T. N. Gerasimova, and E. P. Fokin, *Izv. Sib. Otd. Akad. Nauk SSSR, Ser. Khim. Nauk*, 109 (1976) [*CA* **85**, 77984 (1976)].

¹⁰⁵ T. N. Gerasimova, N. V. Semikolenova, and E. P. Fokin, *Izv. Sib. Otd. Akad. Nauk SSSR, Ser. Khim. Nauk*, 142 (1977) [*CA* **87**, 134160 (1977)].

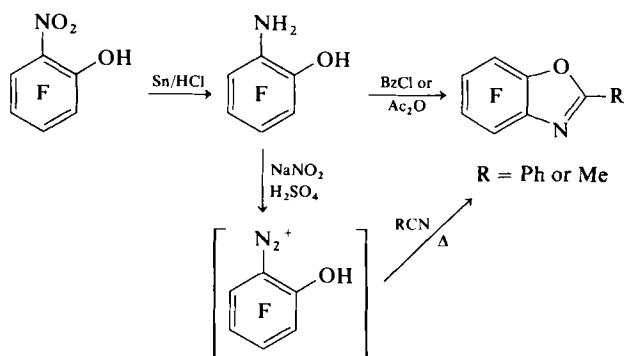
¹⁰⁶ S. Hayashi and N. Ishikawa, *Nippon Kagaku Kaishi* 1319 (1973) [*CA* **79**, 78576 (1973)].

¹⁰⁷ S. Hayashi and N. Ishikawa, *Chem. Lett.*, 99 (1972) [*CA* **76**, 113041 (1972)].

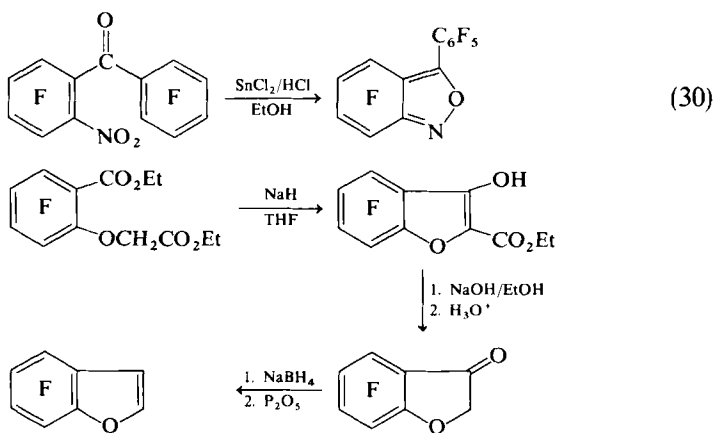
¹⁰⁸ T. V. Fomenko, T. N. Gerasimova, and E. P. Fokin, *Izv. Sib. Otd. Akad. Nauk SSSR, Ser. Khim. Nauk*, 99 (1977) [*CA* **87**, 5778 (1977)].



SCHEME 8



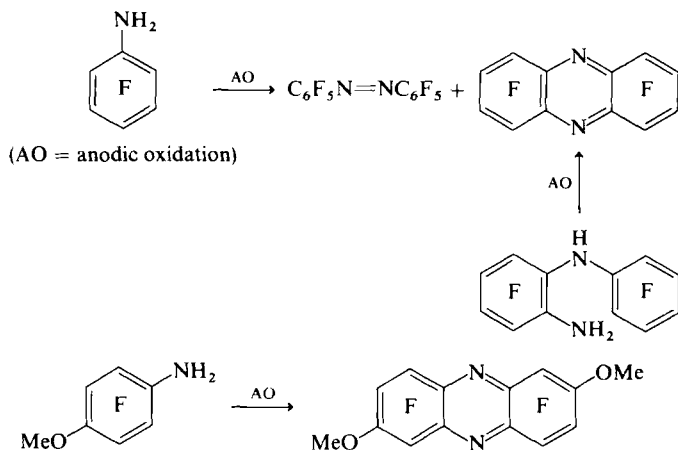
SCHEME 9



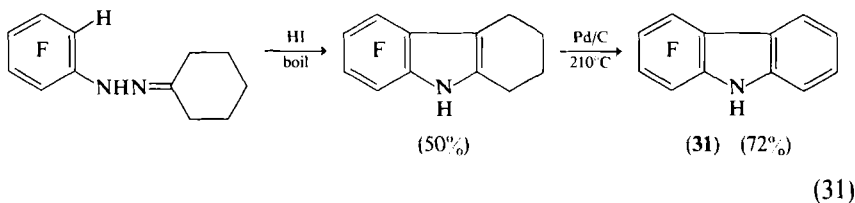
SCHEME 10

Other cyclizations of ortho-difunctional compounds are shown in Schemes 9¹⁰⁹ and 10,¹¹⁰ and in Eq. (30).¹¹¹

c. Miscellaneous. Cyclizations have been observed in the oxidation of fluorinated aromatic amines to phenazine derivatives by electrochemical processes (Scheme 11^{112,113}) and by reaction with lead tetraacetate.¹¹⁴ The classical Fischer indole process can be applied to appropriate polyfluoroaromatic compounds as, for example, in the preparation of tetrafluorocbazole (31) (Eq. 31).¹¹⁵



SCHEME 11



¹⁰⁹ J. M. Birchall, R. N. Haszeldine, J. Nikokavouras, and E. S. Wilks, *J. Chem. Soc. C*, 562 (1971).

¹¹⁰ G. M. Brooke and B. S. Furniss, *J. Chem. Soc. C*, 869 (1967).

¹¹¹ C. M. Jenkins, A. E. Pedler, and J. C. Tatlow, *Tetrahedron* **27**, 2557 (1971).

¹¹² A. G. Hudson, A. E. Pedler, and J. C. Tatlow, *Tetrahedron* **26**, 3791 (1970).

¹¹³ A. G. Hudson, M. L. Jenkins, A. E. Pedler, and J. C. Tatlow, *Tetrahedron* **26**, 5781 (1970).

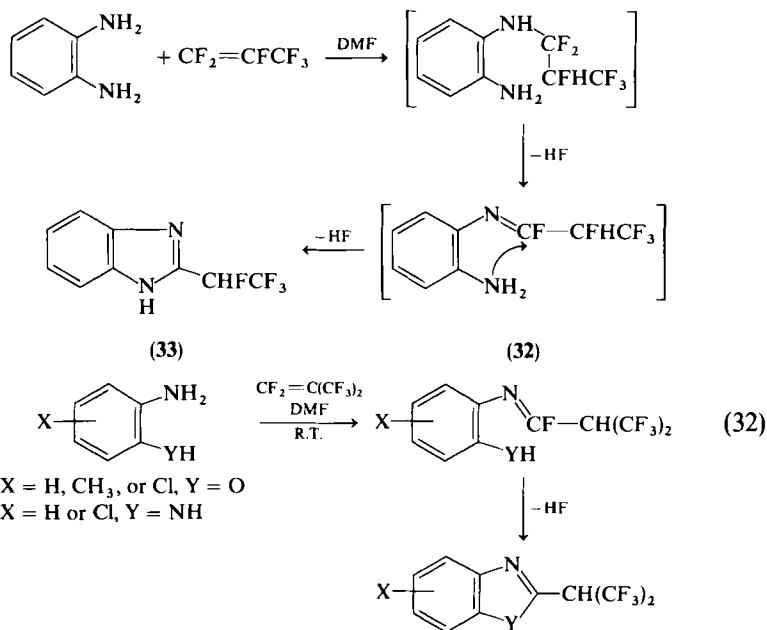
¹¹⁴ J. M. Birchall, R. N. Haszeldine, and J. E. G. Kemp, *J. Chem. Soc. C*, 449 (1970).

¹¹⁵ T. D. Petrova, V. P. Mamaev, and G. G. Yakobson, *Bull. Acad. Sci. USSR, Div. Chem. Sci.*, 609 (1969).

2. Involving Fluorinated Alkenes and Alkynes

For convenience, this section has been formally divided into those reactions involving nucleophilic attack and those involving cycloaddition. However, in some cases this division is arbitrary (e.g., reactions of 1,3-dipoles), and the placement of reactions of this type into either section should not be taken as a firm opinion of mechanism, i.e., concerted or stepwise. In most cases, the mechanistic evidence does not allow a clear distinction to be made.

a. Via Nucleophilic Attack. It would seem obvious that reactions of difunctional nucleophiles with various unsaturated fluorocarbons could give cyclized products. This type of reaction has already been described in Section II,B,1,a. in relation to reactions of fluorinated benzenes, but interesting cyclic products may also be obtained from, for example, fluorinated alkenes. Product **33** from hexafluoropropene with *ortho*-phenylenediamine may be represented as arising from initial addition, accompanied by loss of hydrogen fluoride giving **32**, followed by cyclization.¹¹⁶ Similar cyclizations occur with other difunctional nucleophiles^{116,117} and also involving different fluorinated alkenes (Eq. 32).¹¹⁸

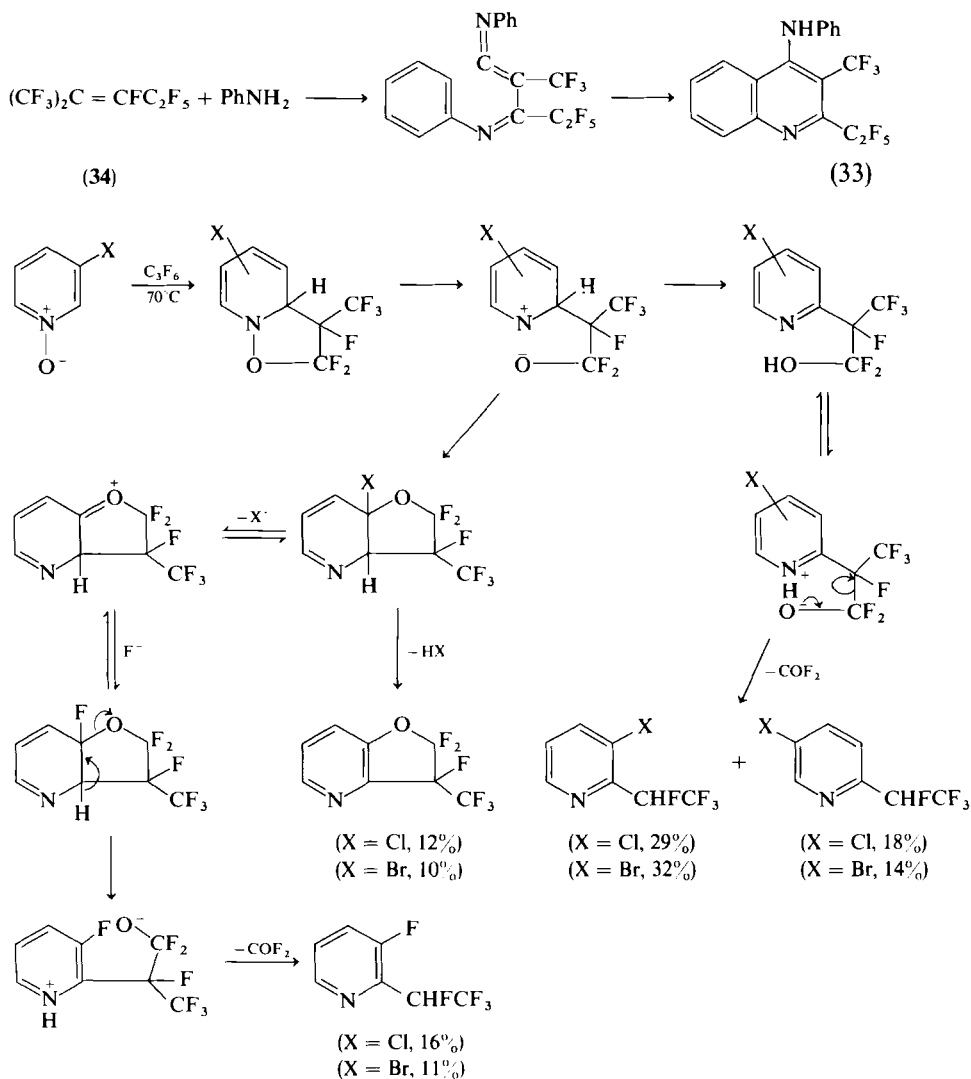


¹¹⁶ N. Ishikawa and T. Muramatzu, *Nippon Kagaku Kaishi* 563 (1973) [*CA* **78**, 147873 (1973)].

¹¹⁷ T. Nakai, N. M. Hassan, and N. Ishikawa, *Bull. Chem. Soc. Jpn.* **50**, 3014 (1977).

¹¹⁸ H. Harada, S. Mizutaki, S. Hayashi, and N. Ishikawa, *J. Fluorine Chem.* **12**, 211 (1978).

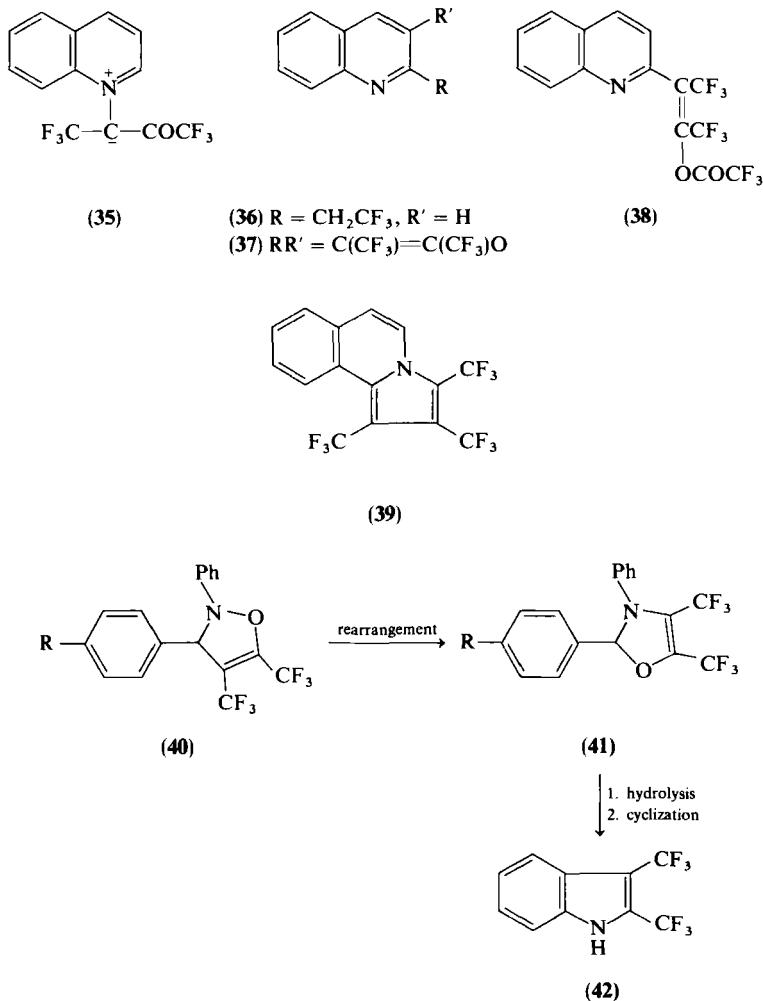
Ketenimines, formed as intermediates in the reactions of aromatic amines with a dimer of hexafluoropropene (34), cyclize in an interesting process that yields perfluoroalkyl derivatives of various heterocyclic systems (Eq. 33).¹¹⁹



SCHEME 12

¹¹⁹ W. T. Flowers, R. N. Haszeldine, C. R. Owen, and A. Thomas, *J. C. S. Chem. Commun.*, 134 (1974).

Reactions of hexafluoropropene with *N*-oxides of various pyridine and quinoline derivatives^{120,121} provide an interesting process for introducing a polyfluoroalkyl group. The mechanism of the process has not been easy to formulate, but the most likely one now seems to be that shown in Scheme 12. The primary step in the addition of *N*-oxides to unsaturated fluorocarbons could be formulated as either a nucleophilic attack or a concerted 1,3-dipolar

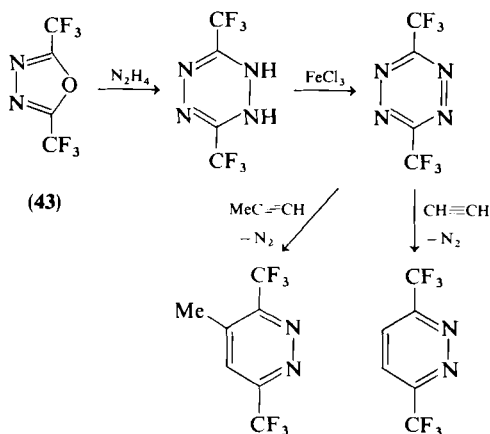


¹²⁰ E. A. Mailey and L. R. Ocone, *J. Org. Chem.* **33**, 3343 (1968).

¹²¹ R. E. Banks, R. N. Haszeldine, and J. M. Robinson, *J. C. S. Perkin I*, 1226 (1976).

cycloaddition. However, the variety of products^{122,123} isolated from reactions of hexafluoro-2-butyne with *N*-oxides of quinoline (35–38) and isoquinoline (39 and many others) suggest that the process, at least in part, involves nucleophilic attack. Compounds 40 and 41 have been obtained from the addition of nitrones to hexafluoro-2-butyne, whereas the indole derivative 42 may be obtained from 41 by hydrolysis and recyclization.¹²⁴

Reaction of the oxadiazole derivative 43 with hydrazine provides the basis for an interesting synthesis of pyridazine derivatives (Scheme 13).¹²⁵



SCHEME 13

b. Cycloaddition Reactions. Reactions of hexafluoro-2-butyne with phosphorus or sulfur could probably be categorized as involving nucleophilic attack, but whatever the mechanism, the reactions provide a direct synthesis of the fluorinated thiophene derivative 44¹²⁶ and the starting point 45¹²⁷ for the preparation of the fascinating diphospha benzene derivative 46 (Scheme 14).^{128,129} An interesting addition of hexafluoro-2-butyne to $\text{N}\equiv\text{SF}$

¹²² Y. Kobayashi, I. Kumadaki, H. Mochizuki, S. Fujino, and T. Kutsuma, *Hukosukan Kagaku Toronkai Koen Yoshishu*, 8th, 1975, 64 (1975) [*CA* **85**, 5474 (1976)].

¹²³ Y. Kobayashi, I. Kumadaki, and S. Fujino, *Heterocycles* **7**, 871 (1977).

¹²⁴ Y. Kobayashi, I. Kumadaki, and T. Yoshida, *Heterocycles* **8**, 387 (1977).

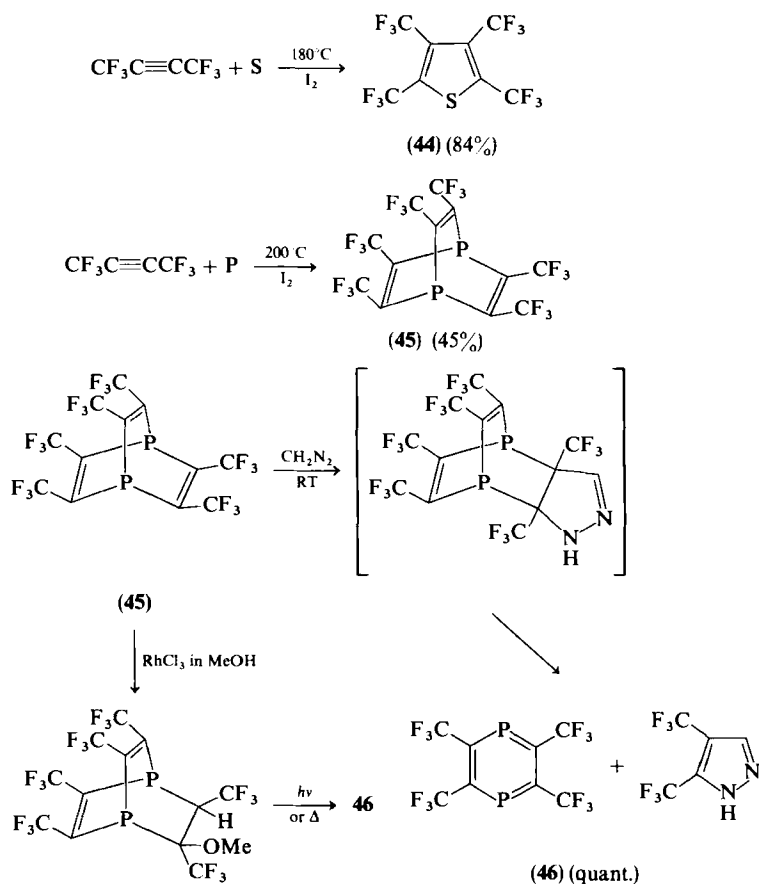
¹²⁵ M. G. Barlow, R. Haszeldine, and J. A. Pickett, *J. C. S. Perkin I*, 378 (1978).

¹²⁶ C. G. Krespan, *J. Am. Chem. Soc.* **83**, 3434 (1961).

¹²⁷ C. G. Krespan, B. C. McKusick, and T. L. Cairns, *J. Am. Chem. Soc.* **82**, 1515 (1960).

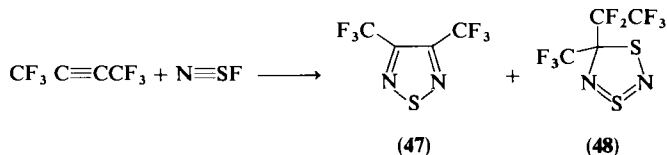
¹²⁸ Y. Kobayashi, I. Kumadaki, A. Ohsawa, and H. Hamana, *Tetrahedron Lett.*, 3715 (1976); 867 (1977).

¹²⁹ Y. Kobayashi, S. Fujino, H. Hamana, I. Kumadaki, and Y. Hanzawa, *J. Am. Chem. Soc.* **99**, 8511 (1977).



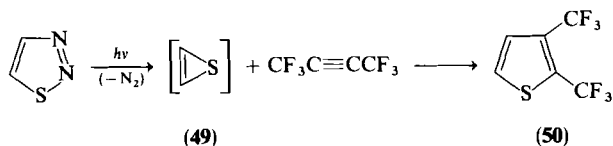
SCHEME 14

occurs,¹³⁰ giving the thiadiazole **47** together with the dithiadiazole **48**, and

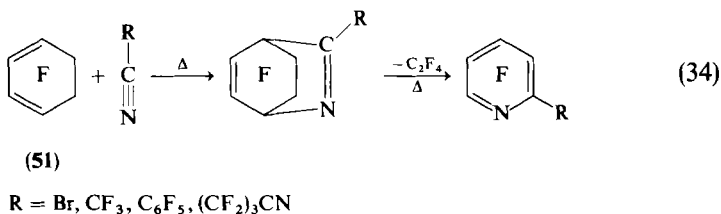


photolysis of 1,2,3-thiadiazole in the presence of hexafluoro-2-butyne gives the thiophene derivative **50**, presumably via addition of the thiirene **49** to the alkyne.¹³¹ Fluorinated alkenes or acetylenes will participate in various

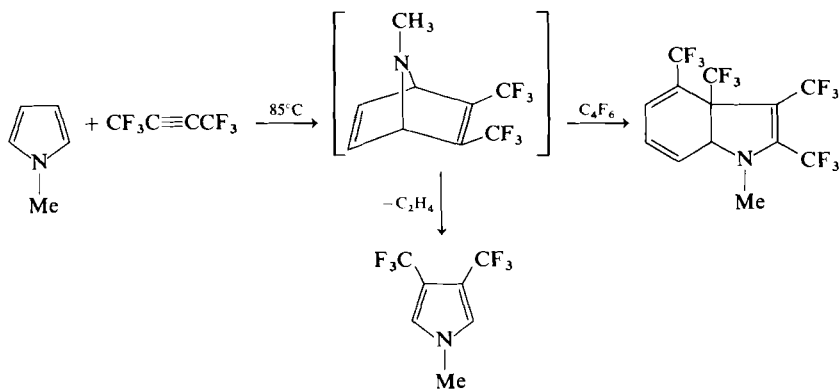
¹³⁰ W. Bludssus and R. Mews, *J. C. S. Chem. Commun.*, 35 (1979).



$(4\pi + 2\pi)$ -cycloadditions with unsaturated systems containing heteroatoms; addition of nitriles to perfluorocyclohexa-1,3-diene (**51**) provides a synthesis of 2-substituted derivatives of perfluoropyridine¹³² (Eq. 34). A variant of this method, involving a bicyclic system, gave perfluoro-3-methylisoquinoline.¹³³ Hexafluoro-2-butyne reacts with the electron-rich *N*-methyl-2-pyrrole¹³⁴ (Scheme 15) and tetrafluorobenzynes may be trapped in a similar



process¹³⁵ (Scheme 16); each of these reactions provides, ultimately, new aromatic heterocycles.



SCHEME 15

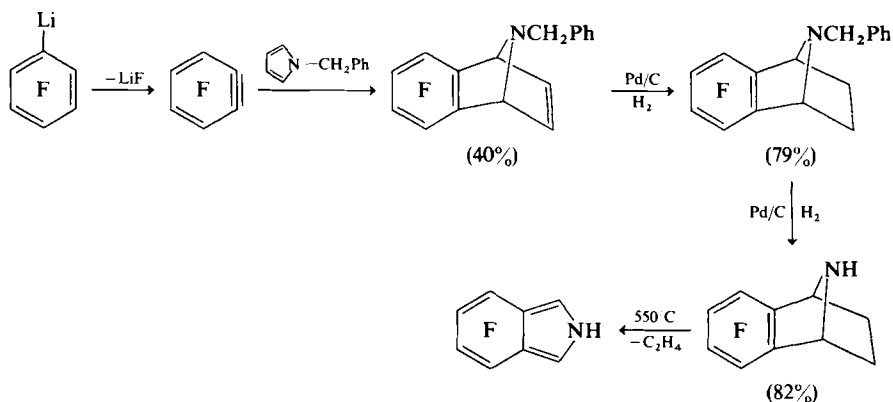
¹³¹ O. P. Strausz, J. Font, E. L. Dedio, P. Kebarle, and H. E. Gunning, *J. Am. Chem. Soc.* **89**, 4805 (1967).

¹³² L. P. Anderson, W. J. Feast, and W. K. R. Musgrave, *J. Chem. Soc. C*, 2559 (1969).

¹³³ W. J. Feast, R. R. Hughes, and W. K. R. Musgrave, *J. Fluorine Chem.* **9**, 271 (1977).

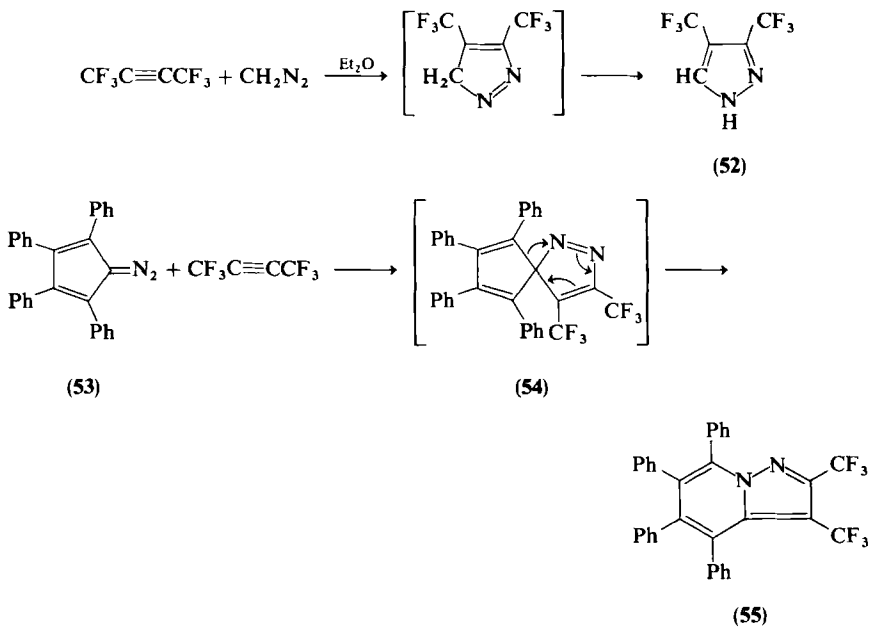
¹³⁴ J. C. Blazejewski, D. Cantacuzene, and C. Wakselman, *Tetrahedron Lett.*, 363 (1975).

¹³⁵ J. Bornstein, D. E. Remy, and J. E. Shields, *Tetrahedron Lett.*, 4247 (1974).



SCHEME 16

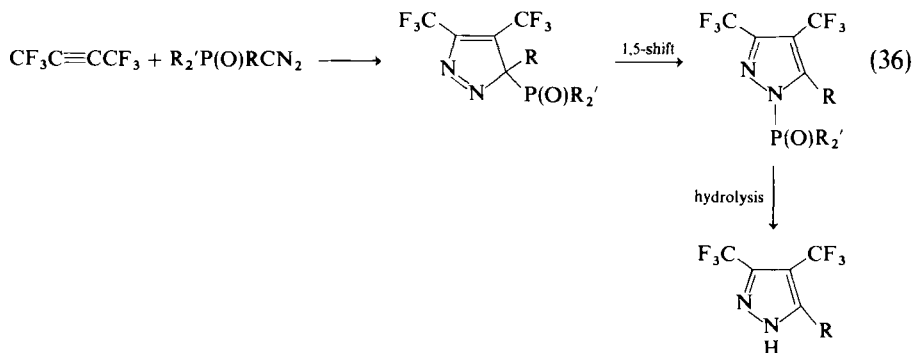
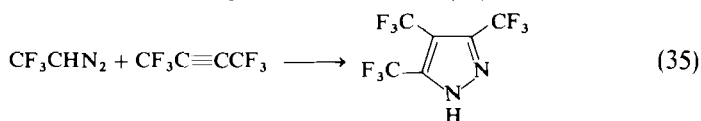
A great wealth of heterocyclic compounds is available through the addition of 1,3-dipoles to unsaturated fluorocarbons. Various additions of diazo-methane occur very readily, especially when perfluoroalkyl groups are attached to the unsaturated centers. Hexafluoro-2-butyne reacts to give **52**^{136,137} while addition of **53** gives the rearranged product **55**, which



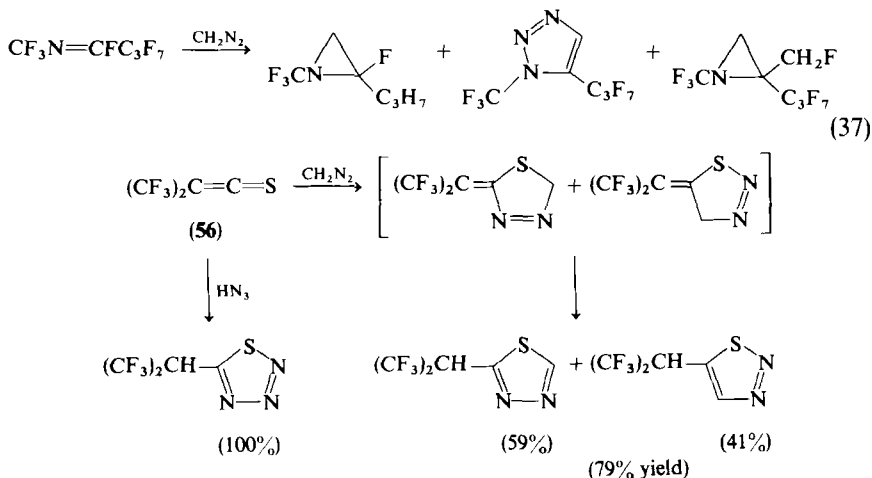
¹³⁶ J. H. Atherton and R. Fields, *J. Chem. Soc. C*, 1507 (1968).

¹³⁷ R. D. Chambers and C. G. P. Jones, unpublished observations.

presumably involves a 1,5-shift from **54**.¹³⁸ Various other additions of diazoalkanes are illustrated in Eqs. (35)^{136,139} and (36).¹⁴⁰ Diazoalkanes



also add readily to various unsaturated fluorocarbons that themselves contain heteroatoms (Eq. 37¹⁴¹ and Scheme 17¹⁴²), and addition of hydrazoic acid to **56** also proceeds in quantitative fashion.¹⁴²



SCHEME 17

¹³⁸ H. Durr and R. Sergio, *Chem. Ber.* **107**, 2027 (1974).

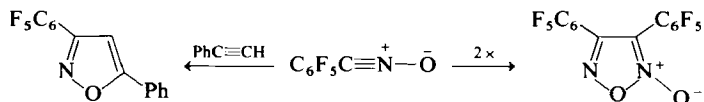
¹³⁹ R. Fields and J. P. Tomlinson, *J. Fluorine Chem.* **13**, 147 (1979).

¹⁴⁰ A. Hartmann and M. Regitz, *Phosphorus* **5**, 21 (1974) [*CA* **83**, 113161 (1975)].

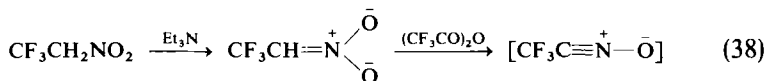
¹⁴¹ P. L. Coe and A. G. Holton, *J. Fluorine Chem.* **10**, 553 (1977).

¹⁴² M. S. Raasch, *J. Org. Chem.* **35**, 3470 (1970).

In certain cases, 1,3-dipoles containing fluorocarbon groups will participate in cycloadditions to unsaturated hydrocarbons (Scheme 18¹⁴³ and Eqs. 38¹⁴⁴ and 39¹⁴⁵⁻¹⁴⁷). The reaction of the nitroalkane derivative **57** probably involves the nitrile oxide **58** as intermediate, since the furoxan product (**59**) corresponds to a dimer.¹⁴⁴ Furoxans have also been obtained

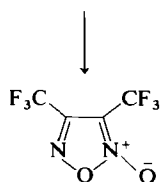


SCHEME 18

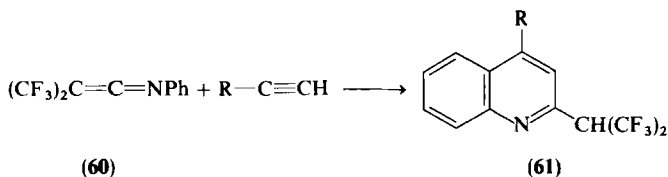
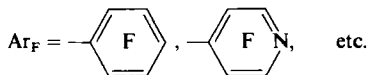
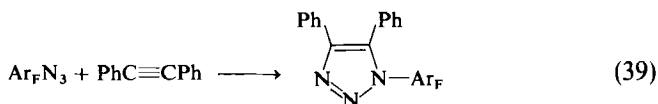


(57)

(58)



(59) (39%)



(60)

(61)

¹⁴³ B. J. Wakefield and D. J. Wright, *J. Chem. Soc. C*, 1165 (1970).

¹⁴⁴ A. M. Krzhizhevski, N. S. Mirzabekyants, Yu. A. Cheburkov, and I. L. Knunyants, *Bull. Acad. Sci. USSR, Div. Chem. Sci.* **23**, 2421 (1974).

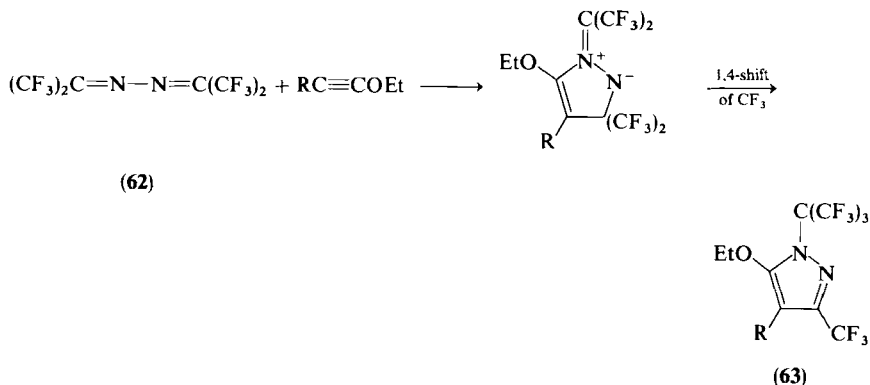
¹⁴⁵ R. E. Banks and G. R. Sparkes, *J. C. S. Perkin I*, 2964 (1972).

¹⁴⁶ R. E. Banks and A. Prakash, *Tetrahedron Lett.*, 99 (1973); *J. C. S. Perkin I*, 1365, 2479 (1974).

¹⁴⁷ R. E. Banks, R. I. Higgons, A. Prakash, M. Rawstron, and G. R. Sparkes, *J. Fluorine Chem.* **9**, 327 (1977).

by reactions of fluorinated diazoalkanes and amines, with NOCl and NO₂, respectively.¹⁴⁸

Fluoroalkylketenimines may be obtained from fluorinated alkenes and **60** undergoes a series of cycloaddition reactions, including formation of the quinoline derivative **61**.¹⁴⁹ Hexafluoroacetone azine (**62**) also reacts with acetylenes¹⁵⁰ and the formation of pyrazoles (**63**) has been formulated as involving the quite novel migration of a trifluoromethyl group.



c. Miscellaneous Furan Derivatives. Several approaches to the synthesis of fluorinated furans have recently appeared, the most direct being those involving the compounds **64** and **65** as precursors. These are relatively accessible, being products obtained by the fluoride ion-induced oligomerization of tetrafluoroethylene, which is conducted on a commercial scale. In a remarkable reaction of **64** with triethylamine in methanol some perfluoro-tetramethylfuran (**67**) is obtained directly. This reaction must involve both cyclization and defluorination and a mechanism has been advanced for the process (Scheme 19).¹⁵¹ Intermediate **66** may be isolated in a reaction of **64** with methanol, induced by pyridine, and may then be effectively defluorinated.

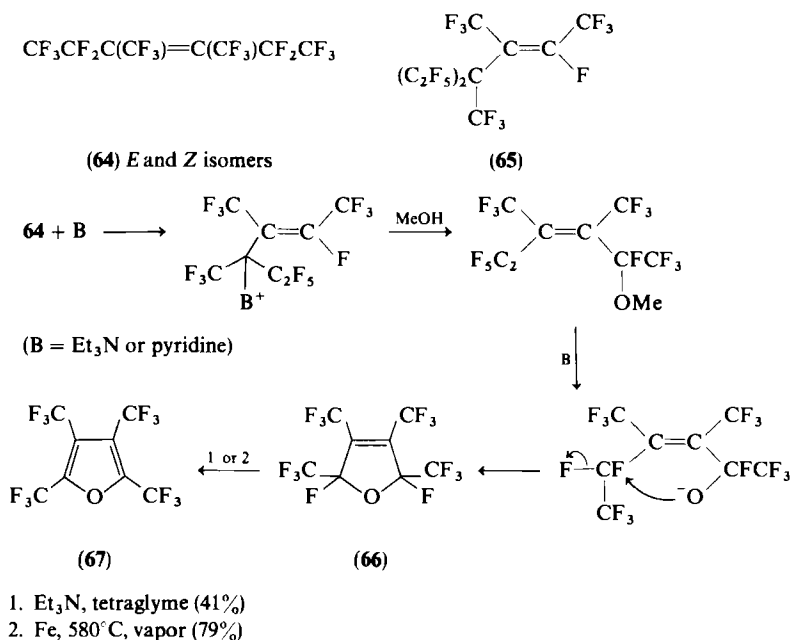
Oligomer **65** may also be converted to the cyclic compound **68** which, on passage over iron or platinum, yields the furan derivatives **67** or **70**, respectively. The different products formed may be accounted for on the

¹⁴⁸ L. W. Kissinger, W. E. McQuiston, and M. Schwartz, *Tetrahedron* **19**, Suppl. 1, 131, 137 (1963).

¹⁴⁹ D. P. Del'tsova, N. P. Gambaryan, Yu. A. Zeifman, and I. L. Knunyants, *Zh. Org. Khim.* **8**, 856 (1972). [*CA* **77**, 34213 (1972)].

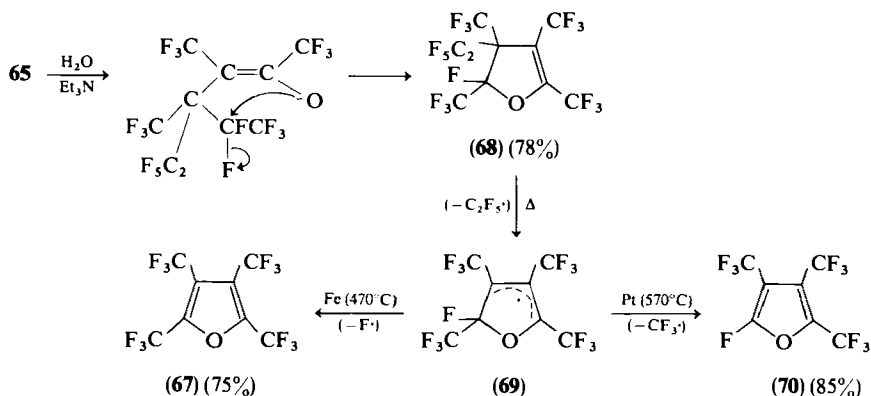
¹⁵⁰ F. Hein, K. Burger, and J. Firl, *Chem. Commun.*, 792 (1979).

¹⁵¹ R. D. Chambers, A. A. Lindley, P. D. Philpot, H. C. Fielding, J. Hutchinson, and G. Whittaker, *J. C. S. Perkin I*, 214 (1979).



SCHEME 19

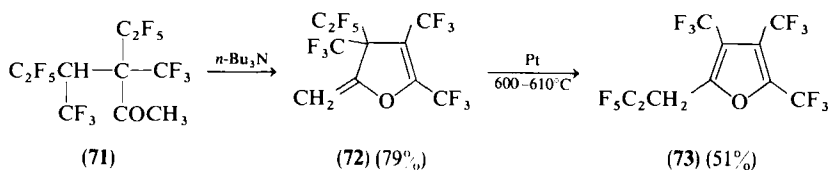
basis of further reaction of the intermediate radical **69**; over iron loss of a fluorine atom predominates, while loss of trifluoromethyl is preferred over platinum.^{151,152}



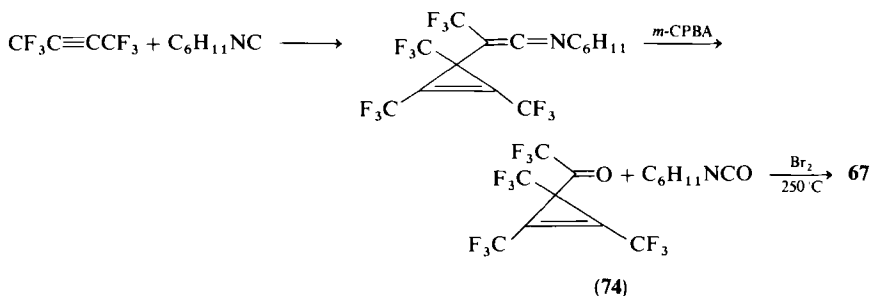
A related route, leading to furan **73**, involves free-radical addition of acetaldehyde to **64**. Adduct **71** undergoes cyclization with base and then the

¹⁵² R. D. Chambers, A. A. Lindley, H. C. Fielding, J. S. Moilliet, and G. Whittaker, *J. C. S. Chem. Commun.*, 475 (1978).

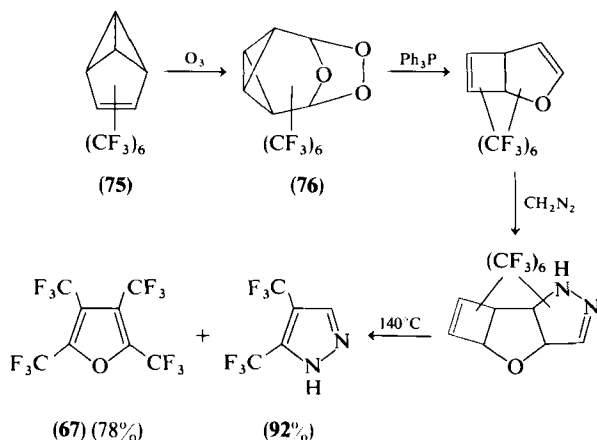
cyclic compound **72** is rearranged to the furan **73** via an interesting 1,3-shift of pentafluoroethyl.¹⁵³



Two other approaches to the furan derivative **67** have been described: (a) from perfluoro-2-butyne and involving the novel cyclopropenyl ketone derivative **74**¹⁵⁴ and (b) by ozonolysis of hexakstrifluoromethylbenzvalene (**75**), followed by treatment of the ozonide (**76**) with triphenylphosphine and diazomethane.¹⁵⁵



m-CPBA = *m*-chloroperbenzoic acid



¹⁵³ R. D. Chambers, S. Bartlett, and N. Kelly, *Tetrahedron Lett.*, 1891 (1980).

¹⁵⁴ C. J. Boriack, E. D. Laganis, and D. M. Lemal, *Tetrahedron Lett.*, 1015 (1978).

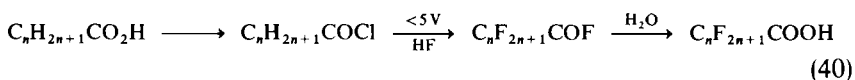
¹⁵⁵ Y. Kobayashi, Y. Hanzawa, Y. Nakanishi, and T. Kashiwagi, *Tetrahedron Lett.*, 1019 (1978).

3. Condensation Reactions of Nitrogen-Containing Compounds

Examples of cyclization in this section are dominated by "classical" methods of synthesis that have been modified to produce appropriate fluorocarbon derivatives. Other authors^{5,156} have discussed this area in more detail than is contained here; we have largely given representative examples rather than comprehensive coverage.

Fluorinated pyridines, diazines, and triazines are easily accessible through processes that involve nucleophilic attack by fluoride ion at the aromatic ring, since the nitrogen atoms in these compounds activate the systems toward nucleophilic attack (see earlier). Conversely, pyrrole-type nitrogen in a five-membered ring deactivates the ring toward such attack, these being π -electron rich systems. Consequently, the method of displacement of chloride by fluoride is, so far, unsatisfactory for five-membered ring systems. Therefore, most of the successful processes described for five-membered rings involve cyclizations of existing fluorocarbon compounds, while cyclizations to produce six-membered rings are those developed principally for triazines.

The dominant source of fluorine compounds as precursors for systems that will take part in these cyclizations are the fluorocarbon carboxylic acids. Many of these compounds are available through electrochemical fluorination processes (Eq. 40),¹⁵⁷ which are carried out on an industrial scale. These can then be converted to standard derivatives which are employed in the various ways described in this section.



a. Five-Membered Rings. i. Containing one nitrogen atom. There are many examples of the formation of oxazole, thiazole, and isoxazole rings from fluorinated precursors,¹⁵⁸⁻¹⁶⁴ and some are illustrated in Eqs. (41),¹⁵⁸ (42),¹⁵⁹ and (43).¹⁶⁰

¹⁵⁶ J. A. Young, in "Fluoropolymers", (L. A. Wall, ed.), Chapter 9. Wiley (Interscience), New York, 1972.

¹⁵⁷ See, e.g., R. D. Chambers, "Fluorine in Organic Chemistry," p. 26, and references contained therein. Wiley (Interscience), New York, 1973.

¹⁵⁸ C. Massyn and A. Cambon, *J. Fluorine Chem.* **5**, 67 (1975).

¹⁵⁹ E. J. Soloski, G. J. Moore, and C. Tamborski, *J. Fluorine Chem.* **8**, 295 (1976).

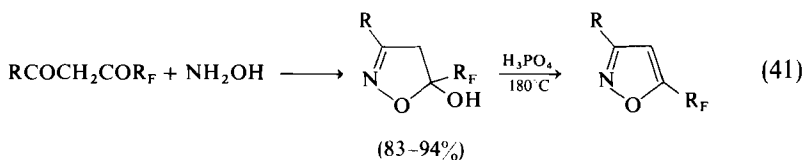
¹⁶⁰ F. N. Jones and R. D. Richardson, U.S. Patent 3,666,769 (1972) [*CA* **77**, 101574 (1972)].

¹⁶¹ K. C. Eapen and C. Tamborski, *J. Fluorine Chem.* **12**, 271 (1978).

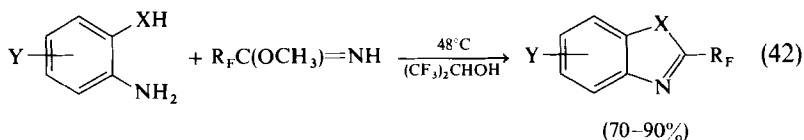
¹⁶² K. C. Joshi, V. N. Pathak, and V. Grover, *Pharmazie* **34**, 68 (1979) [*CA* **91**, 56888 (1979)].

¹⁶³ H. A. Hammouda and N. Ishikawa, *Bull. Chem. Soc. Jpn.* **51**, 3091 (1978).

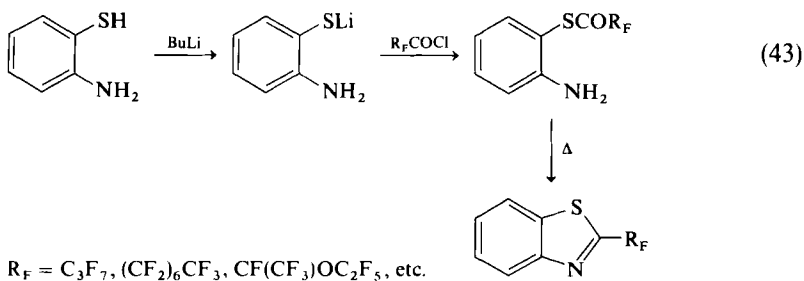
¹⁶⁴ N. Ishikawa and S. Sasaki, *Bull. Chem. Soc. Jpn.* **50**, 2164 (1977).



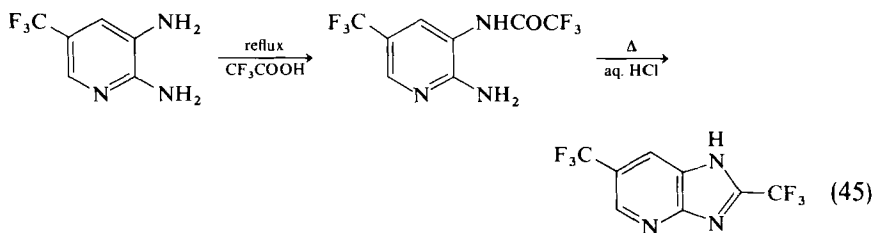
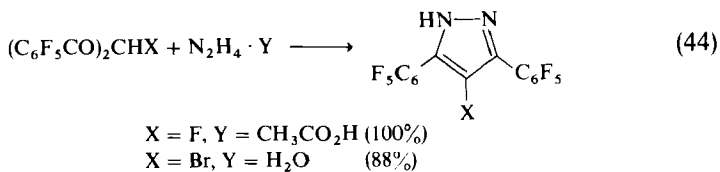
e.g., R = Ph, R_F = C₃F₇, C₅F₁₁, C₇F₁₅



e.g. X = O or S; Y = H, C₃F₇; R_F = C₃F₇



ii. *Containing two nitrogen atoms.* Pyrazoles may be obtained from hydrazine derivatives (Eq. 44)¹⁶⁵ while imidazole derivatives are formed from aromatic diamines^{166,167} (Eq. 45)¹⁶⁶ or as shown in Eq. (46).¹⁶⁸

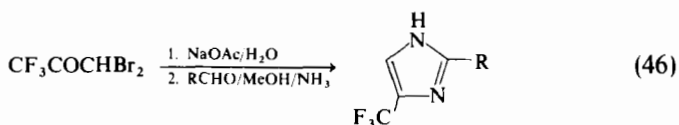


¹⁶⁵ S. A. Osadchii and V. A. Barkhash, *Zh. Org. Khim.* 7, 1215 (1971) [*CA* 75, 98491 (1971)].

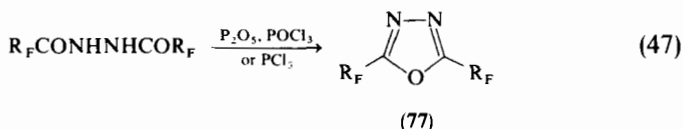
¹⁶⁶ G. O. P. Doherty, U.S. Patent 3,681,369 (1972) [*CA* 77, 140073 (1972)].

¹⁶⁷ Y. C. Tong, U.S. Patent 3,822,261 (1974) [*CA* 81, 120693 (1974)].

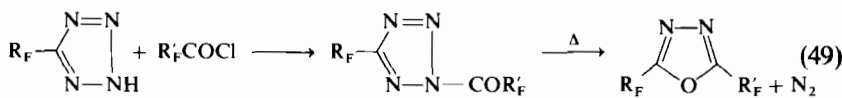
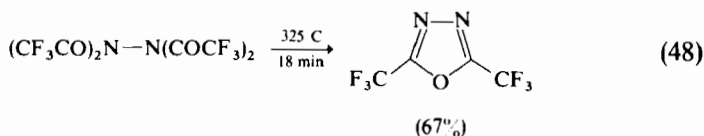
¹⁶⁸ J. J. Baldwin and F. C. Novello, U.S. Patent 4,125,530 (1978) [*CA* 90, 121593 (1979)].



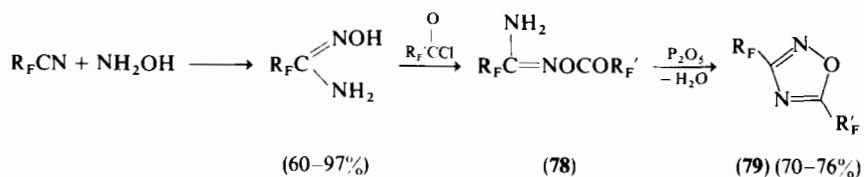
1,3,4-Oxadiazole derivatives (77) are produced by simple dehydration of hydrazine derivatives¹⁶⁹⁻¹⁷³ (Eq. 47) or by pyrolytic elimination of fluoroacyl radicals or nitrogen from appropriate derivatives (Eqs. 48¹⁷⁴ and 49¹⁷⁵).



e.g., $\text{R}_F = \text{CF}_3$, $n\text{-C}_3\text{F}_7$, $n\text{-C}_4\text{F}_9$, $\text{C}_4\text{F}_6\text{Cl}_3$, C_6F_{13} , C_6F_{11} , C_7F_{15} , C_6F_5 , 4-tetrafluoropyridyl



1,2,4-Oxadiazoles (79) are formed from appropriate amidine derivatives (78), themselves obtained from the corresponding nitriles¹⁷⁶⁻¹⁷⁸ (Eq. 50).



e.g., $\text{R}_F = \text{R}'_f = \text{CF}_3$, C_2F_5 , $n\text{-C}_3\text{F}_7$, C_7F_{15}
 $\text{R}_F = n\text{-C}_3\text{F}_7$; $\text{R}'_f = \text{CF}_3$

¹⁶⁹ W. J. Chambers and D. D. Coffmann, *J. Org. Chem.* **26**, 4410 (1961).

¹⁷⁰ H. C. Brown, M. T. Cheng, L. J. Parcell, and D. Pilipovich, *J. Org. Chem.* **26**, 4407 (1961).

¹⁷¹ E. R. Lynch and W. Cummings, British Patent 1,096,600 (1967) [*CA* **68**, 39628 (1968)].

¹⁷² A. T. Prudchenko, S. A. Vereshchagina, V. A. Barkhash, and N. N. Vorozhtsov, *J. Gen. Chem. USSR (Engl. Transl.)* **37**, 2082 (1967).

¹⁷³ R. D. Chambers, C. A. Heaton, and W. K. R. Musgrave, *J. Chem. Soc. C*, 1933 (1968).

¹⁷⁴ J. A. Young, W. S. Durrell, and R. D. Dresdner, *J. Am. Chem. Soc.* **84**, 2105 (1962).

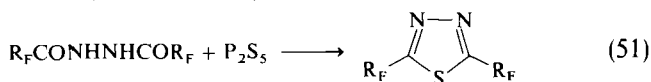
¹⁷⁵ H. C. Brown and R. J. Kassal, *J. Org. Chem.* **32**, 1871 (1967).

¹⁷⁶ H. C. Brown and C. R. Wetzel, *J. Org. Chem.* **30**, 3734 (1965).

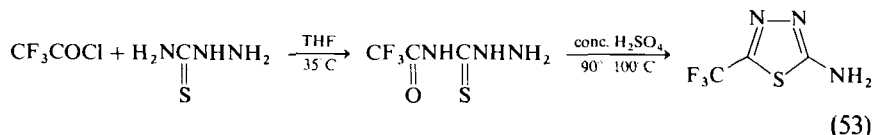
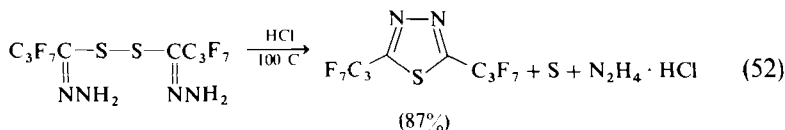
¹⁷⁷ K. L. Paciorek, R. H. Kratzer, J. Kaufman, and R. W. Rosser, *J. Fluorine Chem.* **6**, 241 (1975).

¹⁷⁸ J. P. Critchley and J. S. Pippett, *J. Fluorine Chem.* **2**, 137 (1972).

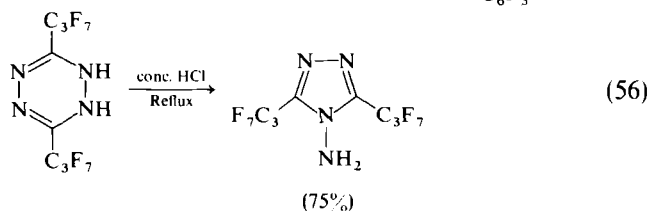
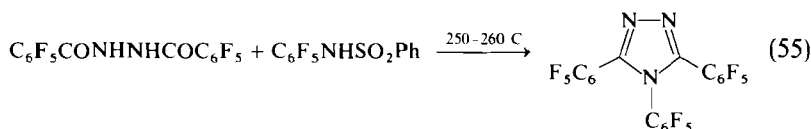
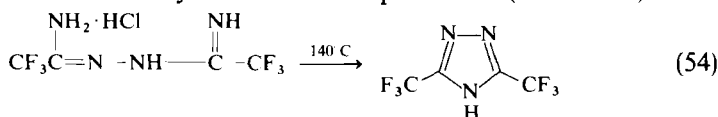
Various procedures are also available for formation of thiadiazole rings (e.g., Eqs. 51,^{169,171-173} 52,¹⁷⁹ and 53¹⁸⁰).



e.g., $\text{R}_F = \text{C}_2\text{F}_5, \text{C}_3\text{F}_7, \text{C}_6\text{F}_5$



iii. *Containing three nitrogen atoms.* Analogous condensation reactions^{171,175,179,181-187} have been used for the synthesis of triazoles and some examples are shown (Scheme 20,¹⁸¹ Eqs. 54,¹⁸² 55,¹⁷¹ 56,¹⁸⁴ 57,¹⁸⁶ and 58¹⁷⁹). Oxadiazoles may also be used as precursors (Scheme 20).



¹⁷⁹ H. C. Brown and R. Pater, *J. Org. Chem.* **30**, 3739 (1965).

¹⁸⁰ R. D. Skiles and K. H. Pilgram, British Patent 1,333,495 (1973) [*CA* **80**, 37115 (1974)].

¹⁸¹ H. C. Brown and M. T. Cheng, *J. Org. Chem.* **27**, 3240 (1962).

¹⁸² H. C. Brown and C. R. Wetzel, *J. Org. Chem.* **30**, 3729 (1965).

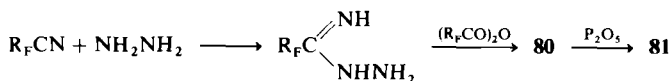
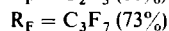
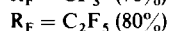
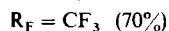
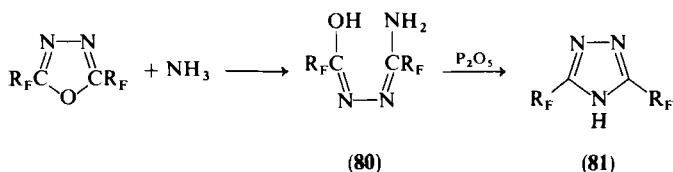
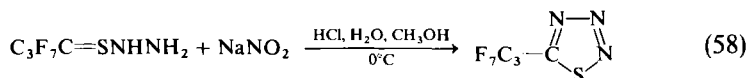
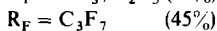
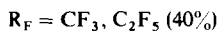
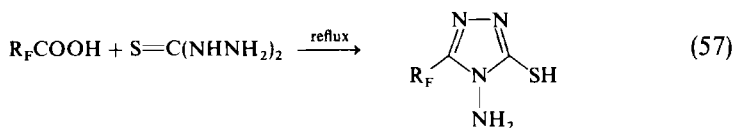
¹⁸³ E. K. Gladding and D. C. Remy, U.S. Patent 3102889 (1963) [*CA* **60**, 4155 (1964)].

¹⁸⁴ H. C. Brown, H. J. Gisler, and M. T. Cheng, *J. Org. Chem.* **31**, 781 (1966).

¹⁸⁵ V. A. Lopyrev, L. P. Sidorova, O. A. Netsetskaya, and M. N. Grinblat, *J. Gen. Chem. USSR (Engl. Transl.)* **39**, 2466 (1969).

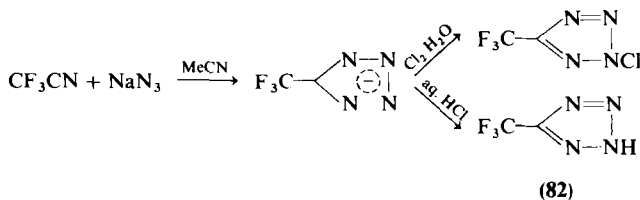
¹⁸⁶ H. Golgolab, I. Lalezari, and L. Hoseini-Gohari, *J. Heterocycl. Chem.* **10**, 387 (1973).

¹⁸⁷ G. Holan and J. J. A. Evans, Australian Patent 499,733 (1979) [*CA* **91**, 74627 (1979)].

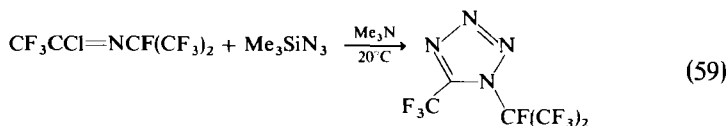


SCHEME 20

iv. *Containing four nitrogen atoms.* Tetrazoles (82) are formed surprisingly readily in reactions of azides with fluorinated nitriles which means that tetrazoles are useful intermediates in the synthesis of other systems, to which some have already been referred. Reactions generally involve alkali metal azides^{175,188} (Scheme 21¹⁸⁸) but the successful use of trimethylsilyl



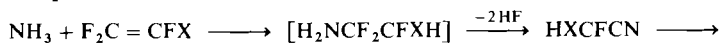
SCHEME 21



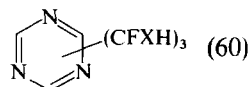
¹⁸⁸ W. P. Norris, *J. Org. Chem.* **27**, 3248 (1962).

azide with imines has also been described (Eq. 59).¹⁸⁹ Reactions of this type are also successful with dinitriles.¹⁹⁰

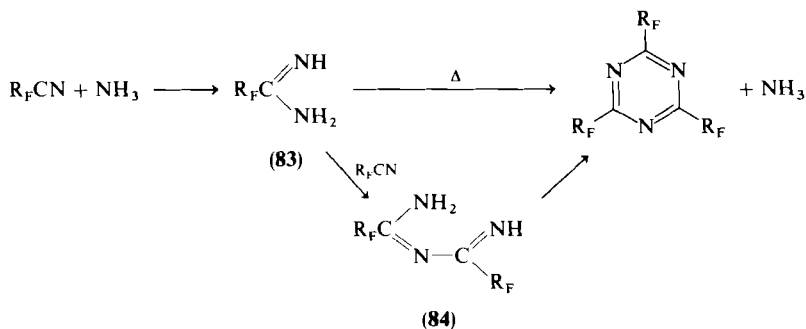
b. Six-Membered Rings. i. Triazines. Much effort has been applied to the synthesis of fluorinated triazines because polymers of these systems are very useful elastomers¹⁵⁶ (see later). The most simple synthesis of a tris(perfluoroalkyl)triazine is the trimerization of a fluorinated nitrile.¹⁹¹ These trimerizations have been claimed to occur remarkably efficiently with a variety of catalysts,^{177,192-198} e.g., phenazine *N*-oxide,¹⁹² halogens,¹⁹³ hydrogen chloride,^{193,194,198} and numerous metal compounds.^{177,192,195-197} Triazines with partly fluorinated alkyl groups have been obtained from nucleophilic attack by ammonia on certain fluorinated alkenes. Nitriles are produced which then trimerize (Eq. 60).¹⁹⁹



X = F, Cl, Br, H



Amidines (**83**) are easily prepared by the addition of ammonia to fluorinated nitriles, and condensation of the amidines is then obtained by heating,



¹⁸⁹ K. E. Peterman and J. M. Shreeve, *J. Fluorine Chem.* **6**, 83 (1975).

¹⁹⁰ E. I. duPont de Nemours & Co., British Patent 988,199 (1965) [*CA* **63**, 700 (1965)].

¹⁹¹ W. L. Reilly and H. C. Brown, *J. Org. Chem.* **22**, 698 (1957).

¹⁹² W. E. Emerson and E. Dorfman, U.S. Patent 3,728,344 (1973) [*CA* **79**, 19743 (1973)].

¹⁹³ N. P. Aktaev, V. A. Pashinin, G. A. Sokol'skii, F. N. Chelobov, and I. L. Knunyants, *Bull. Acad. Sci. USSR, Div. Chem. Sci.*, 2181 (1974).

¹⁹⁴ L. I. Ragulin, A. I. Martynov, G. A. Sokol'skii and L. L. Knunyants, *Bull. Acad. Sci. USSR, Div. Chem. Sci.*, 2074 (1969).

¹⁹⁵ J. L. Zollinger, U.S. Patent 3,470,170 (1969) [*CA* **71**, 124513 (1969)].

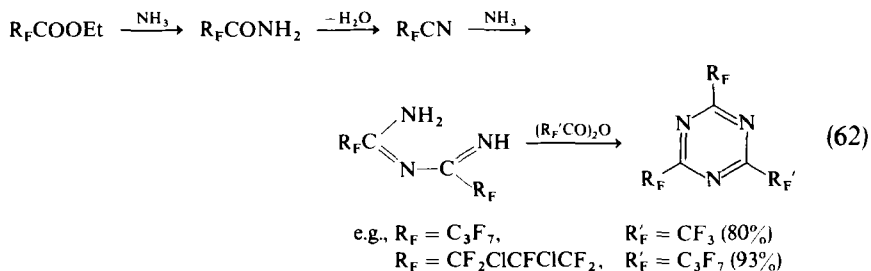
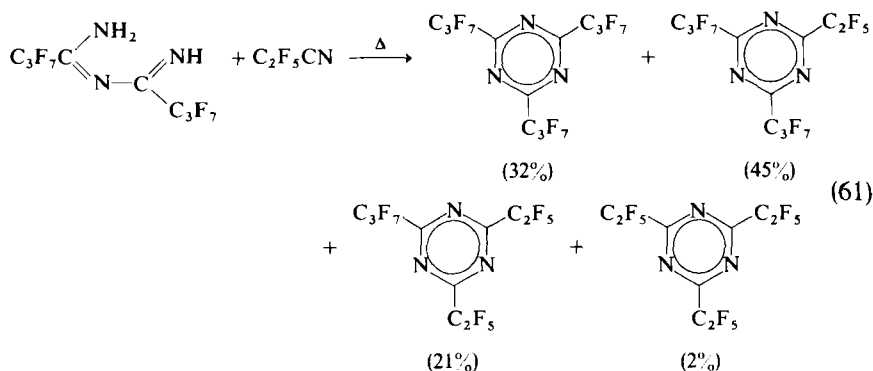
¹⁹⁶ E. Dorfman and W. E. Emerson, French Patent 1,560,303 (1969) [*CA* **71**, 125482 (1969)].

¹⁹⁷ W. E. Emerson and E. Dorfman, French Patent 1,554,658 (1969) [*CA* **71**, 49988 (1969)].

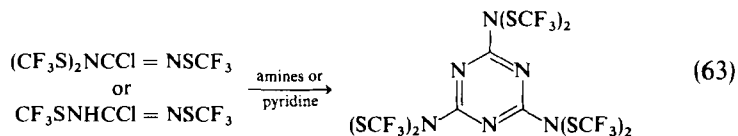
¹⁹⁸ D. Paleta and Z. Prochazkova, *Collect. Czech. Chem. Commun.* **35**, 3452 (1970) [*CA* **74**, 13106 (1971)].

¹⁹⁹ G. W. Rigby, U.S. Patent 2,484,528 (1949) [*CA* **44**, 5925 (1950)].

liberating the ammonia again in a stepwise fashion.^{191,200} The intermediate (84) may be isolated and converted to a triazine.²⁰¹⁻²⁰⁴ Many of the reactions between ammonia and multiple bonds are reversible because a degree of scrambling occurs when different perfluoroalkyl derivatives are used (Eq. 61),²⁰⁵ although this can be minimized in reactions using an anhydride or



acid chloride as the condensing agent (Eq. 62).^{198,203-208} Trimerization of certain imines may also be achieved (Eq. 63).²⁰⁹



²⁰⁰ G. A. Grindahl, W. X. Bajzer, and O. R. Pierce, *J. Org. Chem.* **32**, 603 (1967).

²⁰¹ H. C. Brown, *J. Polym. Sci.* **44**, 9 (1960).

²⁰² P. C. R. Inc., French Patent 2,166,498 (1973) [*CA* **80**, 70845 (1974)].

²⁰³ G. B. Fedorova and I. M. Dolgopolskii, *J. Gen. Chem. USSR (Engl. Transl.)* **39**, 2649 (1969).

²⁰⁴ T. S. Croft and C. E. Snyder, *J. Heterocycl. Chem.* **10**, 943 (1973).

²⁰⁵ H. C. Brown, P. D. Schumann, and J. Turnbull, *J. Org. Chem.* **32**, 231 (1967).

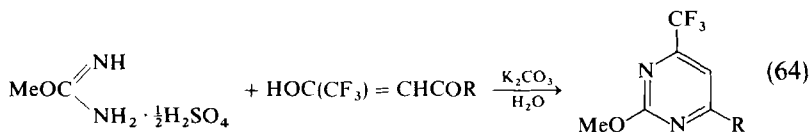
²⁰⁶ M. Tsunoda and K. Omata, Japan Kokai 77/25,785 (1977) [*CA* **87**, 85055 (1977)].

²⁰⁷ J. A. Young and R. L. Dressler, *J. Org. Chem.* **32**, 2237 (1967).

²⁰⁸ G. A. Grindahl, O. R. Pierce, and J. R. Greenwald, U.S. Patent 3,566,835 (1971) [*CA* **74**, 143092 (1971)].

²⁰⁹ A. Haas and V. Plass, *Chem. Ber.* **105**, 2047 (1972).

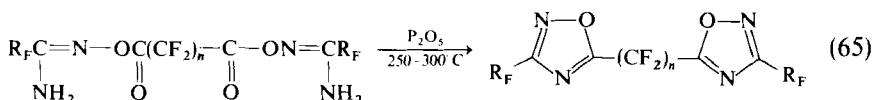
ii. Other systems. Pyrimidines containing a single perfluoroalkyl group are produced in conventional cyclization procedures²¹⁰⁻²¹² (e.g., Eq. 64²¹⁰). Perfluoroalkyl derivatives of isoquinoline²¹³ and related heterocyclic compounds²¹⁴ have also been obtained by cyclization procedures.



c. Oligomers and Polymers. A number of the procedures described for forming rings (e.g., oxadiazoles or triazines) have been applied to the synthesis of polymers, using appropriate difunctional compounds. Some of the resulting systems have very favorable thermal and chemical stability characteristics, but the application of such materials is inevitably limited by cost.

Compounds containing two oxadiazole rings may be obtained from appropriate difunctional compounds^{175,176,178,190,215-217} (e.g., Eq. 65) and a polymer may also be obtained (Eq. 66).¹⁹⁰

A significant research effort has been directed toward fluorinated triazine polymers,^{208,218-221} and examples of the formation of these interesting elastomers of very high thermal stability are given (Eqs. 67²¹⁸ and 68²¹⁹).



²¹⁰ A. Kreutzberger and U. H. Tesch, *Arch. Pharm. (Weinheim, Ger.)* **310**, 56 (1977) [*CA* **86**, 189838 (1977)].

²¹¹ A. Kreutzberger and S. Leyke-Roehling, *Arch. Pharm. (Weinheim, Ger.)* **311**, 884 (1978) [*CA* **90**, 38870 (1979)].

²¹² A. Kreutzberger and S. Leyke-Roehling, *J. Heterocycl. Chem.* **15**, 1097 (1978).

²¹³ R. Pastor and A. Cambon, *J. Fluorine Chem.* **13**, 279 (1979).

²¹⁴ P. M. Hergenrother and M. Hudlicky, *J. Fluorine Chem.* **12**, 439 (1978).

²¹⁵ I. L. Knunyants, M. P. Krasuskaya, and D. P. Del'tsova, *Bull. Acad. Sci. USSR, Div. Chem. Sci.*, 552 (1966).

²¹⁶ Z. I. Mazalova, V. A. Lopyrev, and S. V. Sokolov, *Zh. Org. Khim.* **8**, 531 (1972) [*CA* **77**, 34424 (1972)].

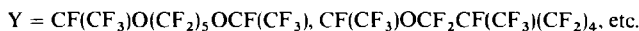
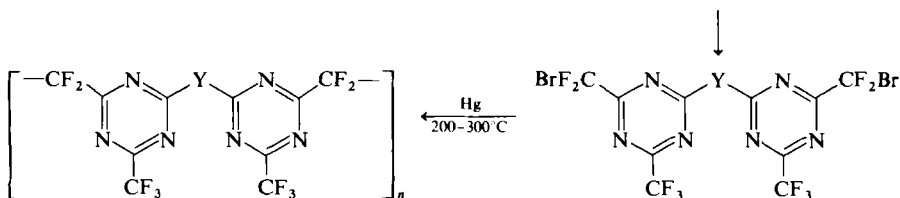
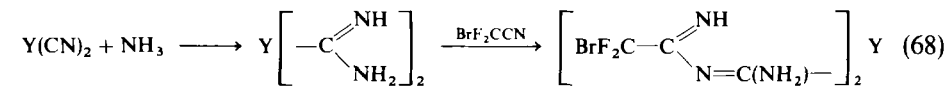
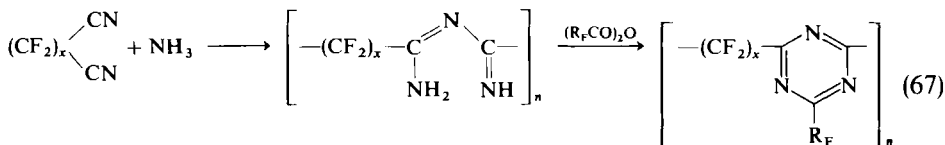
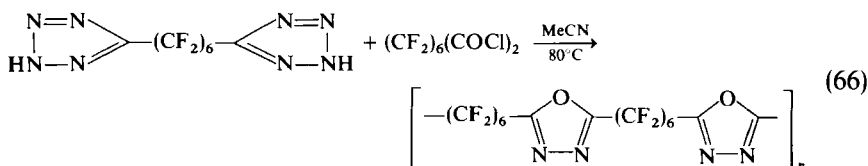
²¹⁷ M. P. Krasuskaya, D. P. Del'tsova, and I. L. Knunyants, *Bull. Acad. Sci. USSR, Div. Chem. Sci.*, 2002 (1965).

²¹⁸ See Ref. 156 for a detailed discussion.

²¹⁹ G. A. Grindahl, J. R. Greenwald, and O. R. Pierce, German Patent 1,953,857 (1970) [*CA* **73**, 56975 (1970)].

²²⁰ Y. K. Kim and O. R. Pierce, German Patent 1,928,050 (1969) [*CA* **72**, 67083 (1970)]; U.S. Patent 3,847,916 (1974) [*CA* **82**, 112436 (1975)].

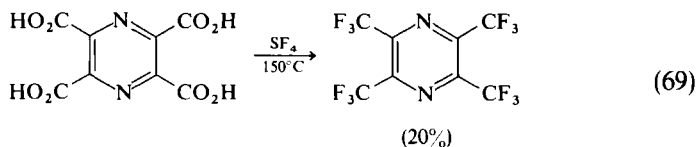
²²¹ Y. K. Kim and O. R. Pierce, *J. Org. Chem.* **34**, 602 (1969).



Related systems are also potentially useful as high thermal stability oils, etc.²²²⁻²²⁵

C. INTRODUCTION OF PERFLUOROALKYL GROUPS

Conversion of carboxyl groups to trifluoromethyl, using sulfur tetrafluoride,²²⁶⁻²²⁹ may be applied to heterocyclic systems (e.g., Eqs. 69²²⁷ and 70²²⁹) but yields are variable.



²²² P. D. Schuman and E. C. Stump, U.S. Patent 3,888,854 (1975) [CA 83, 193398 (1975)].

²²³ T. S. Croft and J. L. Zollinger, U.S. Patent 3,816,416 (1974) [CA 81, 105583 (1974)].

²²⁴ G. B. Fedorova, I. M. Dolgopolskii, and L. G. Parshina, Zh. Org. Khim. 9, 1080 (1973) [CA 79, 53270 (1973)].

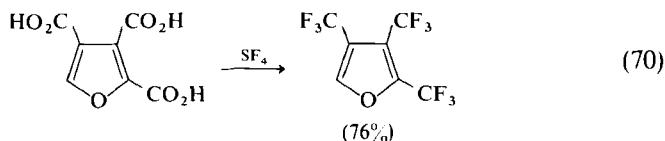
²²⁵ T. S. Croft, J. L. Zollinger, and C. E. Snyder, Ind. Eng. Chem., Prod. Res. Dev. 13, 144 (1974) [CA 81, 13468 (1974)].

²²⁶ W. C. Smith, Angew. Chem., Int. Ed. Engl. 1, 467 (1962).

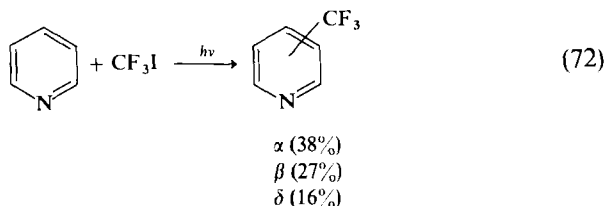
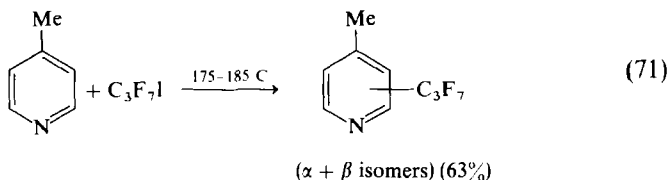
²²⁷ W. R. Hasek, W. C. Smith, and V. A. Engelhardt, J. Am. Chem. Soc. 82, 543 (1960).

²²⁸ Y. Kobayashi, I. Kumadaki, and Y. Hanzawa, Chem. Pharm. Bull. 25, 3009 (1977).

²²⁹ B. V. Lyalin, A. V. Grigorash, L. A. Alekseeva, and L. M. Yagupol'skii, Zh. Org. Khim. 11, 460 (1975) [CA 83, 9849 (1975)].



Thermal reactions of iodo- or bromoperfluoroalkanes with heterocycles have led to perfluoroalkyl derivatives of pyridine²³⁰⁻²³² (Eq. 71)²³¹ and pyrrole,²³³ while more recently it has been demonstrated that photochemical initiation is especially effective (Eq. 72).²³⁴



Polyfluoroalkylcopper compounds may be formed in aprotic media and have been used successfully for the introduction of perfluoroalkyl into various aromatic systems^{228,235,236} (Eqs. 73²³⁶ and 74²²⁸), including pyrimidine derivatives of biological interest.²³⁷⁻²³⁹

²³⁰ L. M. Yagupol'skii, A. G. Galushko, and M. A. Rzhavinskaya, *J. Gen. Chem. USSR (Engl. Transl.)* **38**, 644 (1968).

²³¹ L. M. Yagupol'skii, A. G. Galushko, and V. I. Troitskaya, *J. Gen. Chem. USSR (Engl. Transl.)* **38**, 1692 (1968).

²³² J. H. Tobin, U.S. Patent 4,101,554 (1978) [*CA* **90**, 22831 (1979)].

²³³ I. Cantacuzene, C. Wakselman, and R. Dorme, *J. C. S. Perkin I*, 1365 (1977).

²³⁴ Y. Kobayashi, I. Kumadaki, A. Ohsawa, S. Murakami, and T. Nakano, *Chem. Pharm. Bull.* **26**, 1247 (1978).

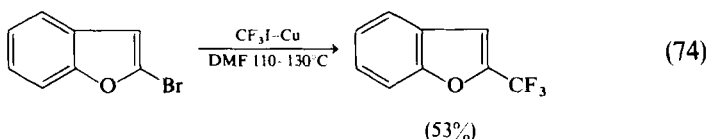
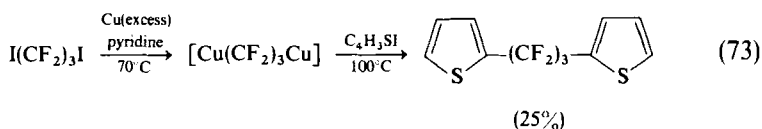
²³⁵ R. Nishiyama, T. Haga, and N. Sakashita, Japan Kokai, Tokyo Koho 79/22371 [*CA* **11**, 56826 (1979)].

²³⁶ V. C. R. McLoughlin and J. Thrower, *Tetrahedron* **25**, 5921 (1969).

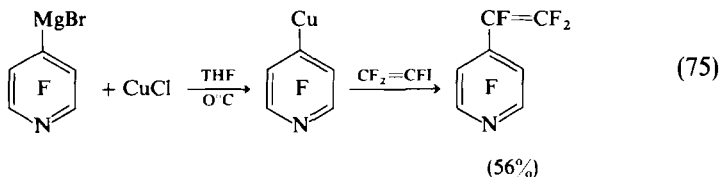
²³⁷ Y. Kobayashi, I. Kumadaki, and K. Yamamoto, *J. C. S. Chem. Commun.*, 536 (1977).

²³⁸ D. Cech, R. Wohlfeil, and G. Etzold, *Nucleic Acids Res., Spec. Publ.* **1**, S5-S8 (1975) [*CA* **85**, 46984 (1976)].

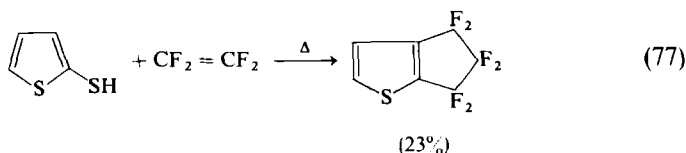
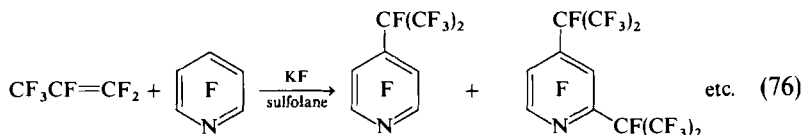
²³⁹ U. R. Polishchuk, G. Ya. Bekker, E. A. Avetisyan, and L. S. German, *Zh. Vses. Khim. O-va* **21**, 222 (1976) [*CA* **85**, 63021 (1976)].



Copper derivatives of polyhalogenopyridines are readily formed²⁴⁰ and have been used to make the corresponding trifluorovinyl derivatives (Eq. 75), but reactions of the copper compounds with iodoperfluoroalkanes do not appear to be successful.



A range of perfluoroalkyl derivatives of highly fluorinated heterocyclic compounds may be obtained in fluoride-induced reactions with fluorinated alkenes²⁴¹ (Eq. 76), but these will be described in more detail later. Copolyrization of thiophenethiol with tetrafluoroethylene gives a fused ring system (Eq. 77).²⁴²



²⁴⁰ E. J. Soloski, W. E. Ward, and C. Tamborski, *J. Fluorine Chem.* **2**, 361 (1972/73).

²⁴¹ R. D. Chambers, J. A. Jackson, W. K. R. Musgrave, and R. A. Storey, *J. Chem. Soc. C*, 2221 (1968).

²⁴² V. E. Platanov, A. M. Maksimov, and G. G. Yakobson, *Izv. Akad. Nauk SSSR, Ser. Khim.*, 2387 (1977) [*CA* **88**, 74250 (1978)].

III. Properties and Reactions

A. PHYSICAL PROPERTIES

Hexafluorobenzene and benzene have very similar boiling points and the generally close relationship between the boiling points of hydrocarbons and the corresponding fluorocarbons is reasonably attributed to a significant reduction in intramolecular forces in the fluorocarbon which offsets increased molecular weight. In comparing a series of azaaromatic compounds with their perfluorocarbon counterparts (Table II),²⁴³ we see that boiling points for the fluorocarbons are actually lower than those of the nonfluorinated analogs. This, in turn, may be attributed to the fact that the base strength in the fluorine derivatives is very considerably reduced. Indeed, super acids are required in order to obtain salts from pentafluoropyridine,²⁴⁴ while methylation of 3,5-dichlorotrifluoropyridine requires methyl fluorosulfonate.²⁴⁵ Using competition methods,²⁴⁴ a comparison of the orders of relative base strengths of some systems has been obtained (Scheme 22); and it was concluded, from a comparison with the orders of the parent compounds, that the most important factor affecting base strength of nitrogen in the fluorinated systems is the number of fluorine atoms that flank the nitrogen atom.

TABLE II
BOILING POINTS OF PERFLUOROAZAAROMATIC COMPOUNDS IN
COMPARISON WITH PARENT COMPOUNDS

Compound	Boiling point ^a (°C)	Boiling point of perfluorinated derivative (°C) ^b
Pyridine	115.5	83.5–84.0
Quinoline	238.0	205
Isoquinoline	243.3	212
Pyridazine	208.0	117
Pyrimidine	123.5–124.0	82–83
Pyrazine	115.5–115.8	53–54

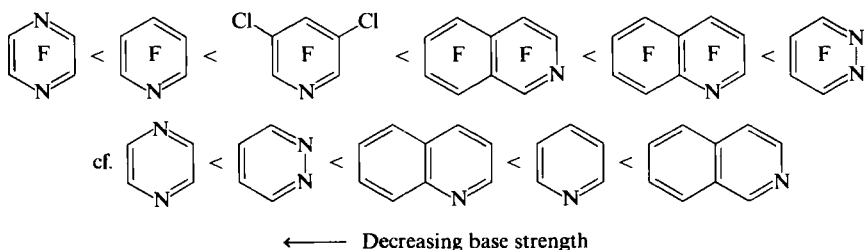
^a See Ref. 243.

^b See Yakobson *et al.*⁴.

²⁴³ R. C. Weast, ed. "Handbook of Chemistry and Physics," 56th ed. Chem. Rubber Publ. Co., Cleveland, Ohio, 1975.

²⁴⁴ S. L. Bell, R. D. Chambers, W. K. R. Musgrave, and J. G. Thorpe, *J. Fluorine Chem.* **1**, 51 (1971/1972).

²⁴⁵ E. Ager and H. Suschitzky, *J. Fluorine Chem.* **3**, 230 (1973).



SCHEME 22

B. INDUSTRIAL APPLICATIONS

At the time of writing, many heterocyclic compounds containing fluorine or fluorocarbon groups are either in use or under active investigation in the fields of chemotherapy and agrochemicals. The list is long and rapidly changing, and detailed discussions are available elsewhere.²⁴⁶ There has been intense activity in bringing into use 4-chlorotrifluoropyrimidine as the basis of various fiber-reactive dyes,²⁴⁷ and the patent literature abounds with claims for the use of various fluorinated systems in this field and for other dyes with high stability.

C. NUCLEOPHILIC SUBSTITUTION

1. Pyridines and Related Systems

With highly fluorinated pyridines and related compounds, evidence indicates the familiar two-step mechanism for nucleophilic aromatic substitution, with the first step (k_1) being rate-limiting (Eq. 78). As with other haloaromatic compounds,²⁴⁸ some of the strongest evidence that this is the case stems from the fact that the mobility order of the halogens is $F \gg Cl, Br, I$, i.e., showing that there can be little carbon-halogen bond breaking in the rate-determining step. In principle, this mobility order need not always apply; and, indeed, there is evidence that *sym*-trichlorotriazine is more reactive than *sym*-trifluorotriazine in a reaction with aniline.²⁴⁹

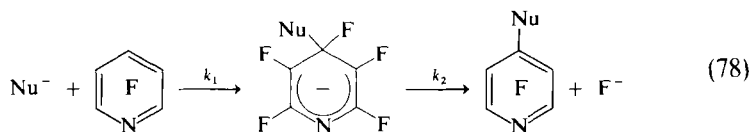
Enormous reactivity increases along the series of perfluorinated derivatives of benzene, pyridine, pyrimidine, and *sym*-triazine, illustrating the dominat-

²⁴⁶ R. Filler, in "Organofluorine Chemicals and their Industrial Applications" (R. E. Banks, ed.), Chapter 6. Ellis Horwood, Chichester, 1979; G. T. Newbold, *ibid.*, Chapter 8.

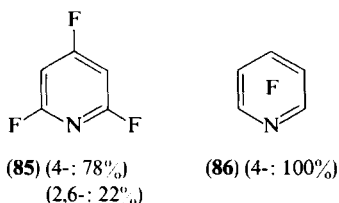
²⁴⁷ W. Harms, in "Organofluorine Chemicals and their Industrial Applications" (R. E. Banks, ed.), Chapter 9. Ellis Horwood, Chichester, 1979; G. Wolfrum, *ibid.*, Chapter 10.

²⁴⁸ See, e.g., R. D. Chambers and S. R. James in "Comprehensive Organic Chemistry" (D. H. R. Barton and W. D. Ollis, eds.), Vol. 1, p. 493, and ref. contained therein. Pergamon, Oxford, 1979.

²⁴⁹ Tran Minh Chinh, J. Kavalek, and M. Vecera, *Collect. Czech. Chem. Commun.* **37**, 3328 (1972) [*CA* **79**, 136155 (1973)].

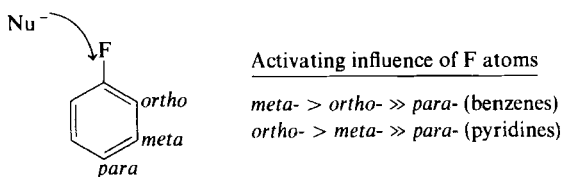


ing influence of ring nitrogens. It is only with highly halogenated systems that problems of orientation arise in nucleophilic aromatic substitution. These are, of course, analogous to the classical problems of electrophilic aromatic substitution in hydrocarbon systems. A comparison of the positions of attack in compounds **85** and **86** (Scheme 23²⁵⁰) reveals that the ring fluorine atoms have an important influence on the orientation of attack. In **85**, the disposition of fluorine atoms for attack at 2-, 6-, or 4-positions is symmetrical, so a preference for attack at the 4-position may be attributed to the orienting effect of nitrogen. Therefore, the fact that attack occurs exclusively at the 4-position in **86** must arise from an additional orienting influence of the fluorine atoms in **86**. It has been possible²⁵⁰⁻²⁵² to distinguish



SCHEME 23. Positions of substitution by aqueous ammonia.

the separate activating influences of fluorine atoms ortho, meta, and para to the center under attack, by comparison of various rate constants for attack on polyfluorobenzenes or -pyridines by aqueous ammonia or methoxide ion (Scheme 24). Therefore, it has been concluded that a fluorine atom para to



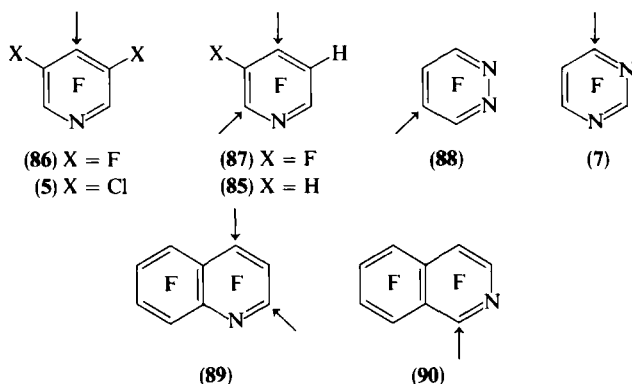
SCHEME 24

the site of attack is slightly deactivating, whereas fluorine atoms ortho and meta are strongly activating, and the relative magnitude of the ortho and meta effects depends on the system. A rationale of these effects has been presented but, whatever the detailed explanation, the experimentally determined

²⁵⁰ R. D. Chambers, J. S. Waterhouse, and D. L. H. Williams, *J. C. S. Perkin II*, 585 (1977).

²⁵¹ R. D. Chambers, D. Close, W. K. R. Musgrave, J. S. Waterhouse, and D. L. H. Williams, *J. C. S. Perkin II*, 1774 (1977).

²⁵² R. D. Chambers, D. Close, and D. L. H. Williams, *J. C. S. Perkin II*, 778 (1980).



SCHEME 25

activating effects provide an understanding of the orientation of attack in a number of situations, i.e., attack occurs so as to maximize the number of activating fluorine atoms. Positions of monosubstitution are indicated by an arrow in the systems shown in Scheme 25.^{31,250,253,254} In pentafluoropyridine (86), attack at the 4-position is activated by four fluorine atoms (two ortho and two meta to the site of attack), whereas attack at the 2-position would be activated by only three fluorine atoms (one ortho and two meta). Similar arguments account for the position of attack in 5, 88, and 7. However, for the systems 85 and 87 there are the same number of fluorine atoms activating attack both at the 4- and 6-positions, and monosubstitution at both sites occurs; a similar situation applies to 89. Of course, this rationale only applies when the nitrogen atom itself is not directing orientation in a highly specific way, as occurs with perfluoroisoquinoline (90).²⁵⁴ Here, attack occurs exclusively at the 1-position, as dictated by the nitrogen, whereas attack at the 3-position would provide the maximum number of activating fluorine atoms. Reactions involving nucleophilic attack on polyfluoropyridines and related systems are referred to in Table III^{31,33,35-37,41,43,44,145,146,249,250,252-295}

²⁵³ R. D. Chambers, J. Hutchinson, and W. K. R. Musgrave, *J. Chem. Soc.*, 5634 (1964).

²⁵⁴ R. D. Chambers, M. Hole, W. K. R. Musgrave, R. A. Storey, and B. Iddon, *J. Chem. Soc. C*, 2331 (1966).

²⁵⁵ R. D. Chambers, J. Hutchinson, and W. K. R. Musgrave, *J. Chem. Soc.*, 3736 (1964).

²⁵⁶ R. E. Banks, J. E. Burgess, W. M. Cheng, and R. N. Haszeldine, *J. Chem. Soc.*, 575 (1965).

²⁵⁷ V. M. Vlasov, V. V. Aksenov, N. E. Akhmetova, G. Z. Mustakimova, and G. G. Yakobson, *Izv. Sib. Otd. Akad. Nauk SSSR, Ser. Khim. Nauk*, 130 (1978) [*CA* **90**, 168411 (1979)].

²⁵⁸ D. W. R. Headford, J. W. Slater, R. L. Sunley, R. D. Bowden, and M. B. Green, German Patent 2,425,239 (1974) [*CA* **83**, 9802 (1975)].

²⁵⁹ R. D. Bowden, M. B. Green, and G. T. Brown, German Patent 2,127,901 (1972) [*CA* **76**, 153615 (1972)].

²⁶⁰ I. N. Rozhkov and N. D. Kuleshova, *Bull. Acad. Sci. USSR, Div. Chem. Sci.* **25**, 1919 (1976).

²⁶¹ C. B. Barlow, C. D. S. Tomlin, G. M. Farrell, P. F. Freeman, J. W. Slater, and J. Clayton, German Patent 2,139,042 (1972) [*CA* **76**, 126795 (1972)].

Footnotes (Continued)

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- ²⁶³ D. Moran, M. Patel, N. A. Tahir, and B. J. Wakefield, *J.C.S. Perkin I*, 2310 (1974).
- ²⁶⁴ I. Collins, S. M. Roberts, and H. Suschitzky, *J. Chem. Soc. C*, 167 (1971).
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- ²⁶⁸ L. N. Markovskii, G. G. Furin, Yu. G. Shermolovich, and G. G. Yakobson, *Bull. Acad. Sci. USSR, Div. Chem. Sci.* **26**, 2628 (1977).
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- ²⁷⁴ B. L. Booth, R. N. Haszeldine, and I. Perkins, *J. Chem. Soc. A*, 927 (1971); *J.C.S. Dalton*, 1843 (1975).
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- ²⁷⁶ J. Wielgat and Z. Domagala, *Rocz. Chem.* **49**, 1039 (1975) [*CA* **83**, 163948 (1975)].
- ²⁷⁷ A. F. Hawkins, D. Riley, R. L. Sunley, and C. D. S. Tomlin, German Patent 2,428,305 (1975) [*CA* **82**, 156090 (1975)].
- ²⁷⁸ R. D. Bowden, M. G. Green, and G. T. Brown, German Patent, 2,130,409 (1972) [*CA* **76**, 140539 (1972)].
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- ²⁸¹ R. D. Bowden and R. Slater, British Patent 1,367,383 (1974); [*CA* **82**, 31266 (1975)].
- ²⁸² R. D. Chambers, D. Lomas, and W. K. R. Musgrave, *J. Chem. Soc. C*, 625 (1968).
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- ²⁸⁵ D. W. Johnson, V. Austel, R. S. Feld, and D. M. Lemal, *J. Am. Chem. Soc.* **92**, 7505 (1970).
- ²⁸⁶ R. E. Banks, D. S. Field, and R. N. Haszeldine, *J. Chem. Soc. C*, 1866 (1969).
- ²⁸⁷ R. E. Banks, R. N. Haszeldine, and J. C. Massey, *J. Fluorine Chem.* **12**, 331 (1978).
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- ²⁹⁵ G. A. Olah, M. Nojima, and I. Kerekes, *Synthesis*, 487 (1973).

TABLE III
EXAMPLES OF NUCLEOPHILIC ATTACK ON PENTAFLUOROPYRIDINE AND SOME RELATED SYSTEMS

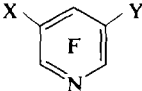





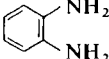

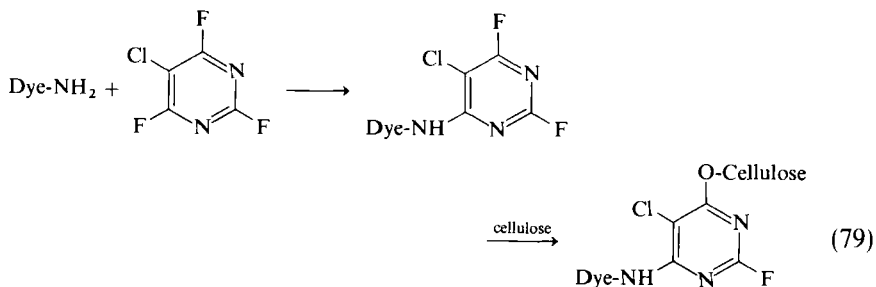
Compound	Reagent	References
	Oxygen nucleophiles (e.g., NaOMe, aq. KOH or <i>t</i> -BuOH, C ₆ F ₅ OH/KF)	252, 253, 255–260
X = Y = F	Nitrogen nucleophiles (e.g., NH ₃ , N ₂ H ₄ · H ₂ O, aminopyridines, pyridine, NaN ₃ ,  , diamines)	145, 146, 250, 255, 256, 261–265
	Sulfur nucleophiles (e.g., KSH, Na ₂ SO ₃ , PhSO ₂ Na, PhSH, C ₆ F ₅ SH)	266, 267
	(EtO) ₃ P	268
	PhLi,  Li	255, 269
	NaI/DMF, LiCl/CF ₂ ClCO ₂ Me	270, 271
	Metal carbonyl anions	272–274
	Me ₃ SnLi	275
	Difunctional nucleophiles	276
X = Y = Cl	aq. KOH or <i>t</i> -BuOH, RCH ₂ OH, CH ₃ CO ₂ K	253, 277, 278
	PhSH	279
	NaI	280
X = F, Y = Cl	NaI, CaCl ₂	280, 281
Perfluoro-3,3'-bipyridyl	Alkoxide ions, NH ₃ , N ₂ H ₄ , MeLi	282
Perfluoro-2,2'-bipyridyl	NaOMe	283
Perfluoroquinoline and -isoquinoline	NaOMe, NH ₃ , N ₂ H ₄	254
	NaOCH ₃ NH ₃ , amines, K phthalimide NaSPh LiCl/DMF Metal carbonyl anions	31 31, 284 31 285 272
Perfluorophthalazine	MeOH, NH ₃	41
	H ₂ O, MeOH PhNH ₂ , MeNH ₂ , Me ₂ NH	33 33
X = F	NaI/DMF, LiI/DMF C ₆ F ₅ MgBr	286, 287 288

TABLE III (Continued)

Compound	Reagent	References
X = H	MeOH; NH ₃ , Me ₂ NH, MeCH=CHLi	35, 289–291
X = Me	aq. KOH, NaOCH ₂ Ph	292, 293
X = Cl, CF ₃ , NO ₂ , CN	MeOH, NH ₃ , MeCH=CHLi	35
Perfluoroquinazoline	NaOMe, NH ₃	43
	NaOMe, (CH ₂ OH) ₂	36
	NH ₃ , N ₂ H ₄ , 	36, 294
	BuLi, MeLi	36
Perfluoroquinoxaline	KOH/ <i>t</i> -BuOH, NaOMe, N ₂ H ₄ ·H ₂ O	44
	H ₂ O, MeOH	37
	NH ₃ , Et ₂ NH, anilines	37, 249
	Carboxylic acids	295
	Metal carbonyl anions	272

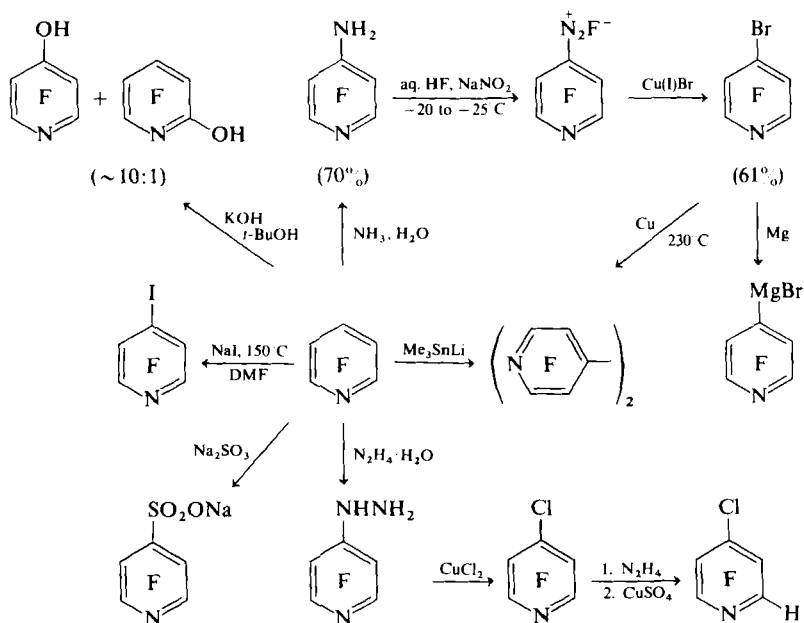
and some useful interconversion reactions of functional derivatives are contained in Scheme 26.²⁹⁶

Very successful fiber-reactive dyes are available by attaching the dyes to fluorinated heterocyclic compounds, which then have sites available for attachment to cellulose (Eq. 79). A detailed review of this subject is now available.²⁴⁷



²⁹⁶ See references in Table III and Ref. 250 and 297.

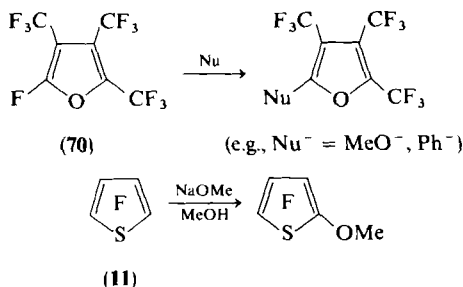
²⁹⁷ R. D. Chambers, J. Hutchinson, and W. K. R. Musgrave, *J. Chem. Soc.*, 5040 (1965).



SCHEME 26. Nucleophilic attack on pentafluoropyridine and some useful interconversion reactions.

2. Five- and Condensed Five-Membered Ring Systems

Perfluorofuran is difficult to handle, tending to polymerize,⁶⁵ but substitution in **70** occurs readily.²⁹⁸ Perfluorothiophene (**11**) undergoes attack ortho to sulfur.⁶⁶ Condensed systems have been investigated in more detail;

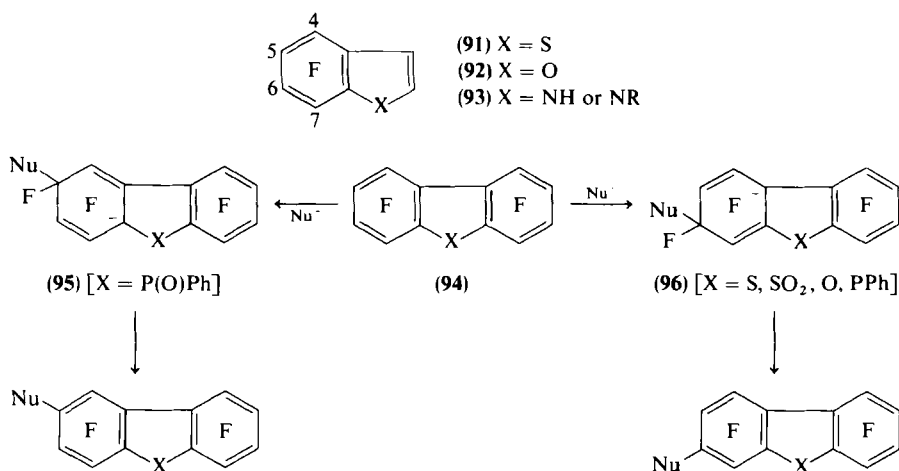


nucleophilic attack on tetrafluorobenzo[*b*]thiophene (**91**) occurs specifically at the 6-position,^{299,77} while a mixture of products is obtained from the

²⁹⁸ R. D. Chambers, A. A. Lindley, and H. C. Fielding, *J. Fluorine Chem.* **12**, 337 (1978).

²⁹⁹ G. M. Brooke and M. A. Quasem, *Tetrahedron Lett.*, 2507 (1967).

furan derivative (92),³⁰⁰ arising from attack at the 4-, 6-, and 7-positions. Indole derivatives (93) undergo attack at the 4-, and 6-positions.³⁰¹



Substitution in dibenzo derivatives (94) can now be mostly explained simply on the basis of whether 95 or 96 is preferred. When X is P(O)Ph, that is, a group whose σ^- value suggests that it is more carbanion stabilizing than pentafluorophenyl, then 95 is preferred. Otherwise, 96 is preferred.^{98,302}

3. Fluoride Ion-Induced Reactions

Carbanions, generated by reaction of fluoride ion with unsaturated fluoro-carbons, may be trapped by reaction with activated polyfluoroaromatic compounds, resulting in the introduction of polyfluoroalkyl groups.³⁰³⁻³⁰⁷ These are, of course, reminiscent of familiar cationic processes and may be thought of as "nucleophilic Friedel-Crafts reactions" (Eqs. 80 and 81).³⁰⁷

³⁰⁰ G. M. Brooke, B. S. Furniss, and W. K. R. Musgrave, *J. Chem. Soc. C*, 580 (1968).

³⁰¹ T. D. Petrova, T. I. Savchenko, O. C. Kukovinets, and G. G. Yakobson, *Izv. Sib. Otd. Akad. Nauk SSSR, Ser. Khim. Nauk*, 104 (1973) [*CA* **79**, 42275 (1973)].

³⁰² R. D. Chambers and D. J. Spring, *Tetrahedron* **27**, 669 (1971).

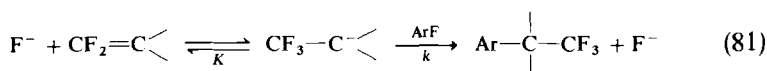
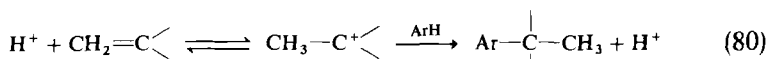
³⁰³ See, e.g., Chambers,² p. 296 for earlier refs. and detailed examples.

³⁰⁴ R. D. Chambers, J. Hutchinson, and P. D. Philpot, *J. Fluorine Chem.* **9**, 15 (1977), and earlier parts of a series.

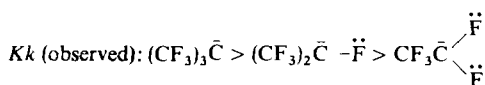
³⁰⁵ C. J. Drayton, W. T. Flowers, and R. N. Haszeldine, *J. C. S. Perkin I*, 1029 (1975), and references contained.

³⁰⁶ N. I. Delyagina, E. Ya. Pervova, B. L. Dyatkin, and I. L. Knunyants, *Zh. Org. Khim.* **8**, 851 (1972) [*CA* **77**, 19266 (1972)].

³⁰⁷ R. D. Chambers, R. A. Storey, and W. K. R. Musgrave, *Chem. Commun.*, 384 (1966).



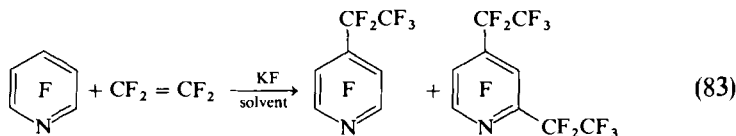
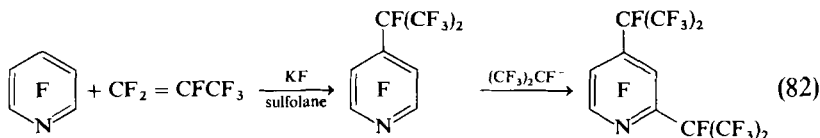
Intrinsically, the situation is quite complicated because observed reactivity is the product of an equilibrium constant K for generation of a carbanion and a rate constant k (Eq. 81) which depends on the reactivity of the carbanion involved. The order of reactivity is that shown in Scheme 27, and the fact that perfluoro-*tert*-butyl is the most efficient anion in polyfluoroalkylation processes indicates that the equilibrium concentration of anion is the



(← increasing anion stability)

SCHEME 27

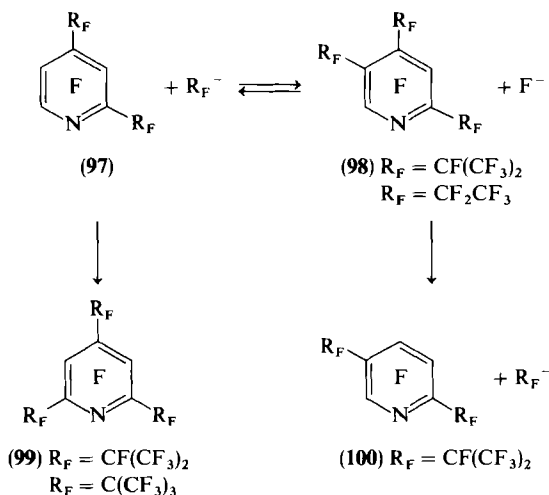
dominating factor governing efficiency of reaction. The stability of the anions increases as electron-pair repulsions are reduced. Examples of mono- and disubstitutions are shown in Eqs. (82)²⁴¹ and (83).³⁰⁸



Polysubstitution involves various factors because (a) after two polyfluoroalkyl groups are present these may control the site of further attack, (b) some of the reactions are reversible, and (c) substitution at the site most activated to attack sometimes results in crowding. This can lead to a competition between kinetic and thermodynamic control of reaction products³⁰⁹ (Scheme 28). For example, further attack on the disubstituted compound (97) occurs

³⁰⁸ H. C. Fielding, British Patent 1,133,492 (1968).

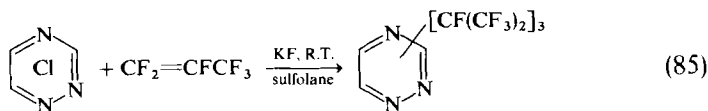
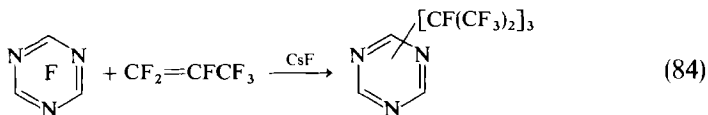
³⁰⁹ S. L. Bell, R. D. Chambers, M. Y. Gribble, and J. R. Maslakiewicz, *J. C. S. Perkin I*, 1716 (1973), and references therein.



SCHEME 28

preferentially at the 5-position with the least crowded anions, but with perfluoroisopropyl the product obtained depends on conditions because, at higher temperatures in the presence of fluoride ion, rearrangement of **98** to **99** ($\text{R}_F = \text{perfluoroisopropyl}$) occurs. A 2,5-disubstituted product (**100**) is also observed.

Only in the case of triazines^{310–312} is complete substitution obtained readily (Eqs. 84,³¹⁰ and 85³¹²), although a pentasubstitution product has been observed from pentafluoropyridine, using tetrafluoroethylene.^{308,313} In



some cases, the triazine system itself competes very effectively for fluoride ion since stable anions (**101**) have been characterized.³¹⁴

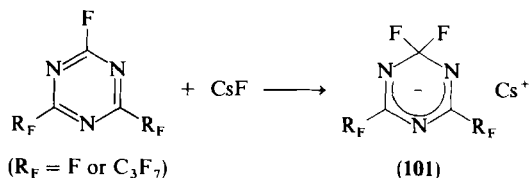
³¹⁰ R. L. Dressler and J. A. Young, *J. Org. Chem.* **32**, 2004 (1967).

³¹¹ W. R. Deem, British Patent 1,148,676 (1969) [*CA* **71**, 49994 (1969)].

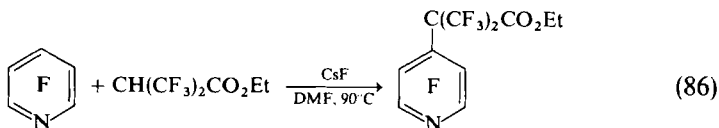
³¹² R. D. Chambers, W. K. R. Musgrave, and D. E. Wood, *J. C. S. Perkin I*, 1978 (1979).

³¹³ M. G. Barlow, R. N. Haszeldine, and J. G. Dingwall, *J. C. S. Perkin I*, 1542 (1973).

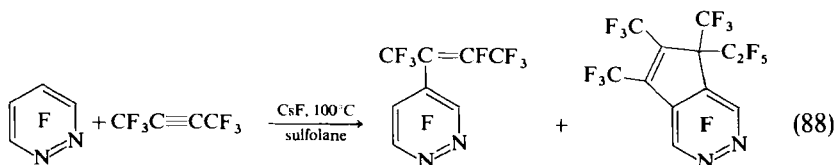
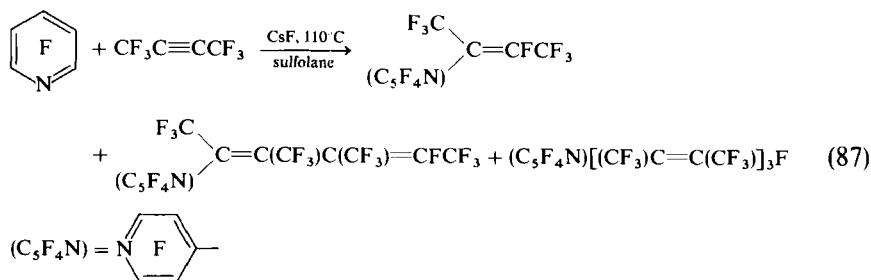
³¹⁴ R. D. Chambers, P. D. Philpot, and P. L. Russell, *J. C. S. Perkin I*, 1605 (1977).



Fluorinated anions have also been generated from appropriate hydrogen-containing compounds, using fluoride ion as a base (Eq. 86).³¹⁵



Hexafluoro-2-butyne adds to activated perfluoroaromatic compounds giving corresponding unsaturated side chains, or with the pyridazine system an interesting cyclization occurs (Eqs. 87 and 88).³¹⁶



4. Reactions Involving Side Chains

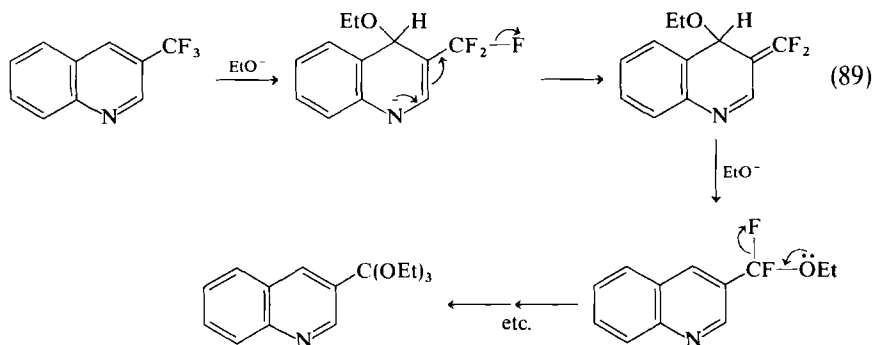
An interesting mechanism for displacement of fluorine from side chains has been identified³¹⁷ and is illustrated by 3-trifluoromethylquinoline (Eq. 89). Perfluoroalkyl groups have also been found to behave as leaving groups

³¹⁵ V. M. Vlasov and G. G. Yakobson, *Zh. Org. Khim.* **10**, 888 (1974) [*CA* **81**, 13357 (1974)].

³¹⁶ R. D. Chambers, S. Partington, and D. B. Speight, *J. C. S. Perkin I*, 2673 (1974).

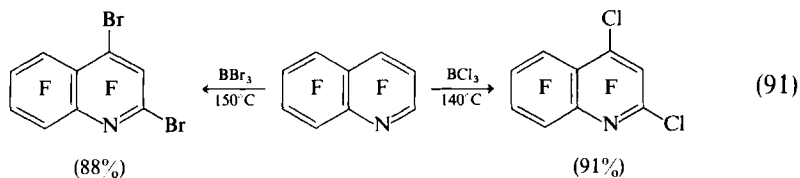
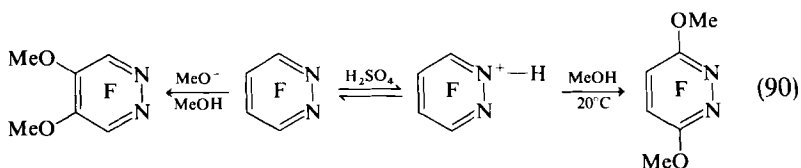
³¹⁷ Y. Kobayashi and I. Kumadaki, *Acc. Chem. Res.* **11**, 197 (1978), and references therein.

in reactions of some heteroaromatic derivatives with sodium amide³¹⁷ or ammonia.³¹⁸



D. REACTIONS WITH ELECTROPHILIC REAGENTS

Perfluoroaromatic nitrogen heterocyclic compounds are very weak bases, but various substitution reactions can be induced by protonic or Lewis acids³¹⁹⁻³²¹ and interesting contrasts in orientation achieved since attack ortho to nitrogen is often preferred under these conditions (Eqs. 90³²¹ and 91³²⁰).



Oxidation of perfluoropyridine and related compounds to their *N*-oxides has not been described, although there is evidence for their intermediacy in

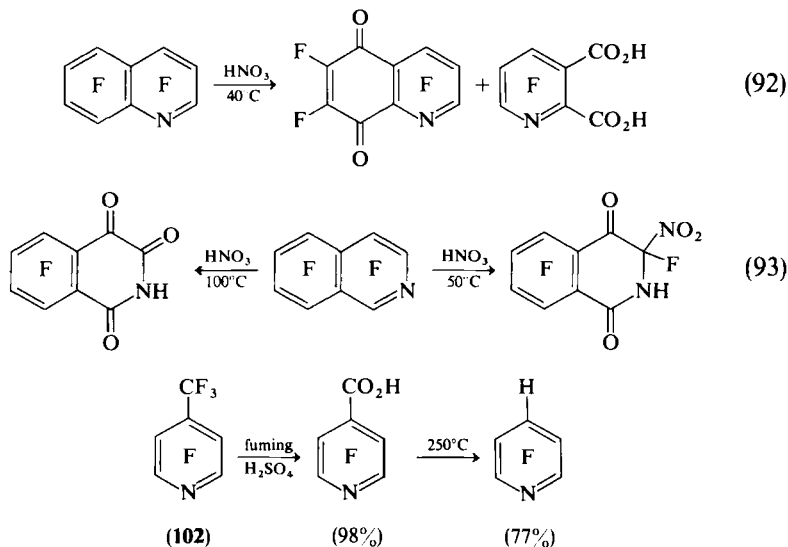
³¹⁸ M. I. Bognitskii, G. B. Fedorova, and I. M. Dolgopolskii, *Zh. Vses. Khim. O-va*, **24**, 101 (1979) [*CA* **90**, 168553 (1979)].

³¹⁹ R. D. Chambers, M. Hole, W. K. R. Musgrave, and J. G. Thorpe, *J. Chem. Soc.*, 61 (1971).

³²⁰ W. K. R. Musgrave, *Chem. Ind.*, (London) 943 (1969).

³²¹ R. D. Chambers, J. A. H. MacBride, and W. K. R. Musgrave, *J. Chem. Soc. C*, 2989 (1968).

the formation of hydrolysis products.³²² However, oxidative displacement of fluorine or ring opening of perfluoroquinoline (Eq. 92)³²³ and -isoquinoline (Eq. 93)³²⁴ occurs with nitric acid. Acid hydrolysis of trifluoromethyl occurs in **102**³²⁵ and oxidation of other groups has been investigated.^{326,327}



E. ADDITION REACTIONS AND RADICAL PROCESSES

Further fluorination of perfluoroaromatic compounds^{328,329} occurs quite smoothly in many cases, using cobalt trifluoride and related reagents (Eq. 94). These reactions are of course much easier to control than fluorinations of the corresponding parent compounds containing hydrogen; and the dimeric compound (**103**), obtained from perfluoropyrimidine, presents some of the best evidence for a radical cation process for this type of reaction (Scheme 29). Even direct fluorination of pentafluoropyridine, with fluorine of low

³²² G. E. Chivers and H. Suschitzky, *J. Chem. Soc. C*, 2867 (1971).

³²³ P. Sartori, K. Ahlers, and H. J. Frohn, *J. Fluorine Chem.* **7**, 363 (1976).

³²⁴ P. Sartori, K. Ahlers, and H. J. Frohn, *J. Fluorine Chem.* **8**, 457 (1976).

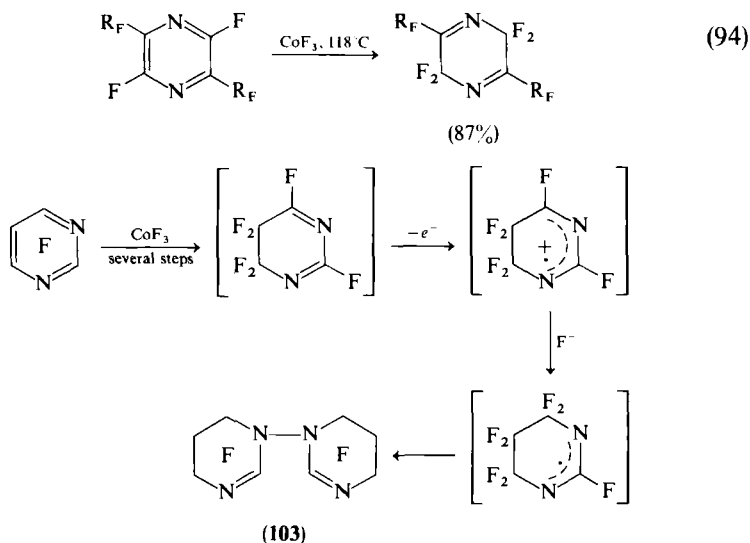
³²⁵ R. E. Banks, J. E. Burgess, and R. N. Haszeldine, *J. Chem. Soc.*, 2720 (1965).

³²⁶ S. M. Roberts and H. Suschitzky, *J. Chem. Soc. C*, 1485 (1969).

³²⁷ P. B. Domenico, U.S. Patent 3,651,066 (1972) [*CA* **77**, 48271 (1972)].

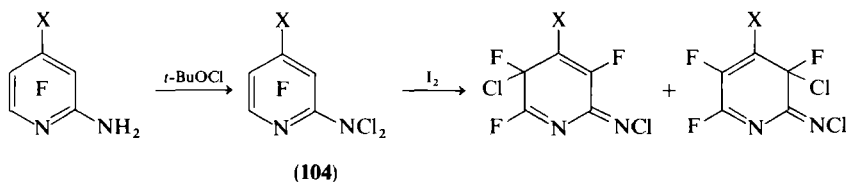
³²⁸ R. D. Chambers, D. T. Clark, T. F. Holmes, W. K. R. Musgrave, and I. Ritchie, *J. C. S. Perkin I*, 114 (1974).

³²⁹ R. D. Chambers, R. D. Hercliff, and W. K. R. Musgrave, *J. C. S. Chem. Commun.*, 304 (1978).



SCHEME 29

oxygen content, can be controlled, giving a mixture of products including a glassy solid thought to be a mixture of oligomers.³³⁰ Addition of chlorine and bis(trifluoromethyl)nitroxide to pentafluoropyridine³³¹ occurs and some dimeric products are obtained in corresponding reactions of chlorine with perfluorodiazines.³³² An adduct $(\text{CF}_2\text{NCl})_3$, obtained by the addition of ClF to trifluoro-*sym*-triazine, is reported to be a useful fluorinating agent.³³³ Bromine and chlorine add 2,5- to tetrafluorofuran.⁶⁵ An interesting migration of chlorine from the side chain of **104** to the ring is catalyzed by iodine.³³⁴



[e.g., X = H, Cl, $\text{CF}(\text{CF}_3)_2$]

³³⁰ I. J. Hotchkiss, R. Stephens, and J. C. Tatlow, *J. Fluorine Chem.* **10**, 541 (1977).

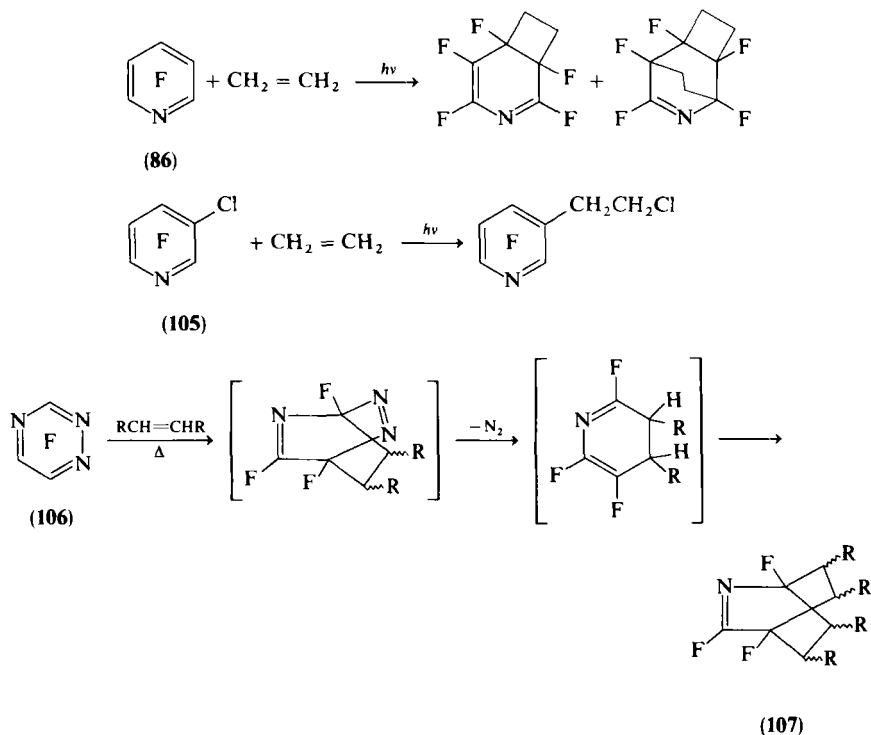
³³¹ R. E. Banks, W. M. Cheng, R. N. Haszeldine, and G. Shaw, *J. Chem. Soc. C*, 55 (1970).

³³² R. D. Chambers, W. K. R. Musgrave, and P. G. Urben, *J. Fluorine Chem.* **5**, 275 (1975).

³³³ R. L. Kirchmeier, G. H. Sprenger, and J. M. Shreeve, *Inorg. Nucl. Chem. Lett.* **11**, 699 (1975).

³³⁴ R. E. Banks, M. G. Barlow, J. C. Hornby, and M. Mamaghani, *J. Fluorine Chem.* **14**, 183 (1979).

Photochemical additions of alkenes to aromatic compounds are now well established and similar additions to pentafluoropyridine (**86**) occur,³³⁵ whereas a novel insertion into the carbon–chlorine bond occurs with **105**, in a process that does not appear to involve tetrafluoropyridyl radicals.³³⁶ It has also been demonstrated recently that Diels–Alder additions occur with



the 1,2,4-triazine **106**, giving bis-adducts (**107**) with cycloalkenes.³³⁷ Photochemically induced reactions of some alcohols³³⁸ or cyclohexane³³⁹ lead to radical attack specifically at the 4-position in pentafluoropyridine (**86**) to give, for example, **108**. Reductive additions to fluorinated *sym*-triazines also occur on irradiation in hydrocarbon solvents.³⁴⁰

³³⁵ M. G. Barlow, D. E. Brown, and R. N. Haszeldine, *J. C. S. Perkin I*, 363 (1978).

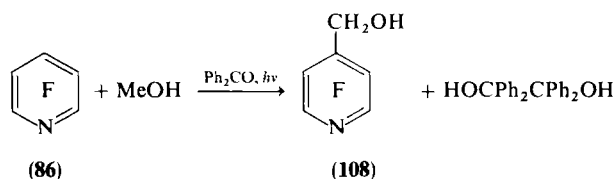
³³⁶ M. G. Barlow, R. N. Haszeldine, and J. R. Langridge, *J. C. S. Chem. Commun.*, 608 (1979).

³³⁷ M. G. Barlow, R. N. Haszeldine, and D. J. Simpkin, *J. C. S. Chem. Commun.*, 658 (1979).

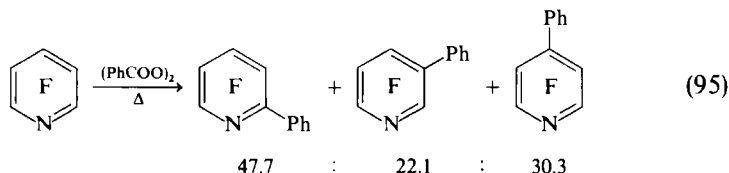
³³⁸ B. Sket and M. Zupan, *J. Heterocycl. Chem.* **15**, 527 (1978).

³³⁹ B. Sket and M. Zupan, *Synthesis*, 760 (1978).

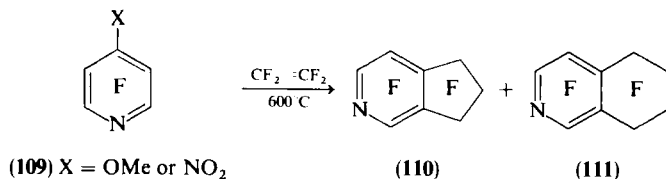
³⁴⁰ Y. Kobayashi, A. Ohsawa, and M. Honda, *Chem. Pharm. Bull.* **21**, 1575 (1973).



Various pyrolytic processes lead to products that arise from substitution in the ring,^{341,342} and many can be simply formulated as radical displacements of fluorine (Eq. 95),³⁴¹ although reaction of chlorofluoropyridines with bromine at high temperatures leads to displacement of chlorine.³⁴³



Copolyrolysis of tetrafluoroethylene and the pyridine derivatives **109** under flow conditions gave bicyclic products **110** and **111**.³⁴⁴ In a sealed system,



reaction occurs at high temperature between pentafluoropyridine and polytetrafluoroethylene, and the process has been rationalized as involving initial addition of difluorocarbene.^{345,346} A corresponding reaction with potassium fluoride in the absence of polytetrafluoroethylene³⁴⁷ is more difficult

³⁴¹ P. H. Oldham, G. H. Williams, and B. A. Wilson, *J. Chem. Soc. B*, 1346 (1970).

³⁴² T. A. Nadervel, V. Sass, L. G. Parshina, G. B. Fedorova, I. M. Dolgapol'ski, and S. V. Sokolov, *Zh. Org. Khim.* **15**, 1095 (1979) [*CA* **91**, 73912 (1979)].

³⁴³ R. D. Bowden and T. Seaton, German Patent 2,241,562 (1973) [*CA* **78**, 159438 (1973)].

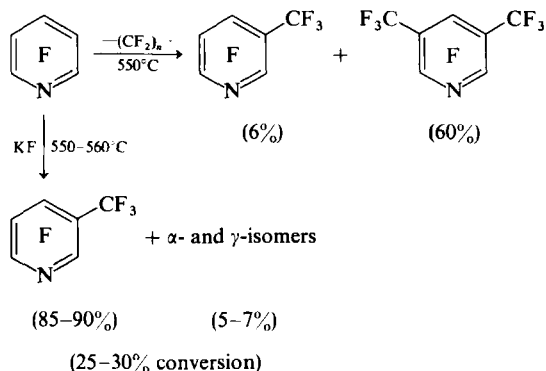
³⁴⁴ G. G. Yakobson, V. E. Platanov, G. G. Furin, N. G. Malyuta, and N. V. Ermolenko, *Bull. Acad. Sci. USSR, Div. Chem. Sci.* **20**, 2491 (1971).

³⁴⁵ R. D. Chambers, R. P. Corbally, T. F. Holmes, and W. K. R. Musgrave, *J. C. S. Perkin I*, 109 (1974).

³⁴⁶ V. E. Platanov, N. V. Ermolenko, and G. G. Yakobson, *Izv. Sib. Otd. Akad. Nauk SSSR, Ser. Khim. Nauk*, 117 (1978) [*CA* **90**, 6196 (1979)].

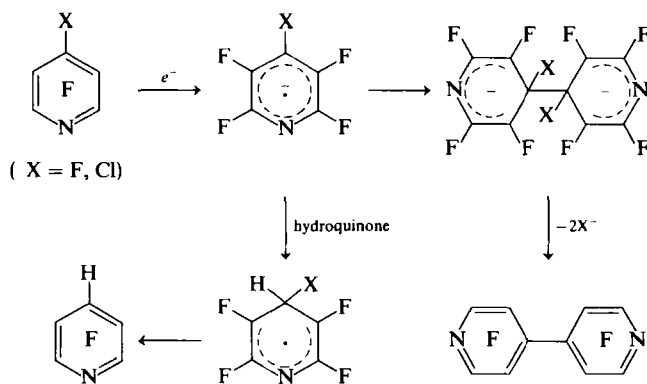
³⁴⁷ V. E. Platanov, N. V. Ermolenko, and G. G. Yakobson, *Bull. Acad. Sci. USSR, Div. Chem. Sci.*, 2685 (1970).

to understand (Scheme 30) as is the formation of trifluoromethyl derivatives in the pyrolysis of tetrafluoropyrimidine.³⁵



SCHEME 30

Radical-anions are generated by electrochemical reduction of fluorinated pyridines (Scheme 31³⁴⁸) and other heterocycles.³⁴⁹ Radical-anions have also been produced from polyfluoropyridines by X-ray irradiation and studied by ESR using matrix isolation techniques. It was concluded that crossover of σ^* and π^* -orbitals occurs.³⁵⁰



SCHEME 31

³⁴⁸ R. D. Chambers, D. T. Clark, C. R. Sargent, and F. G. Drakesmith, *Tetrahedron Lett.*, 1917 (1979).

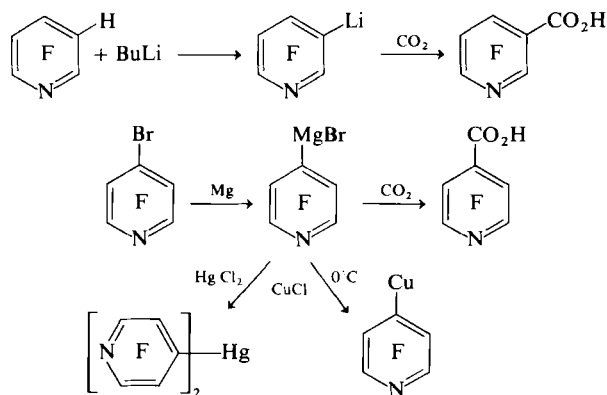
³⁴⁹ D. M. W. Van den Ham, G. F. S. Harrison, A. Spaans, and D. Van der Meer, *Recl. Trav. Chim. Pays-Bas* **94**, 168 (1975).

³⁵⁰ M. B. Yim, S. DiGregorio, and D. E. Wood, *J. Am. Chem. Soc.* **99**, 4260 (1977).

F. REACTIVE INTERMEDIATES

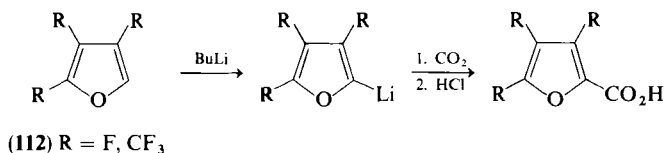
1. Organometallics

Fluorocarbon organometallic compounds have been discussed more generally elsewhere.³⁵¹ Lithium derivatives and Grignard reagents^{352-354,240,270,280,297} may be obtained as indicated in Scheme 32. These compounds are unstable relative to elimination of metal fluoride, but can be used at lower temperatures for a variety of transformations. Attempts to generate corresponding lithium or magnesium derivatives of perfluorinated diazines resulted in tars.^{286,355}



SCHEME 32

Furan derivatives (112) are also metallated with butyllithium.^{65,356}



³⁵¹ R. D. Chambers, "Fluorine in Organic Chemistry," Chapter 10. Wiley (Interscience), New York, 1973.

³⁵² R. D. Chambers, F. G. Drakesmith, J. Hutchinson, and W. K. R. Musgrave, *Tetrahedron Lett.*, 1705 (1967).

³⁵³ R. D. Chambers, F. G. Drakesmith, and W. K. R. Musgrave, *J. Chem. Soc.*, 5045 (1965).

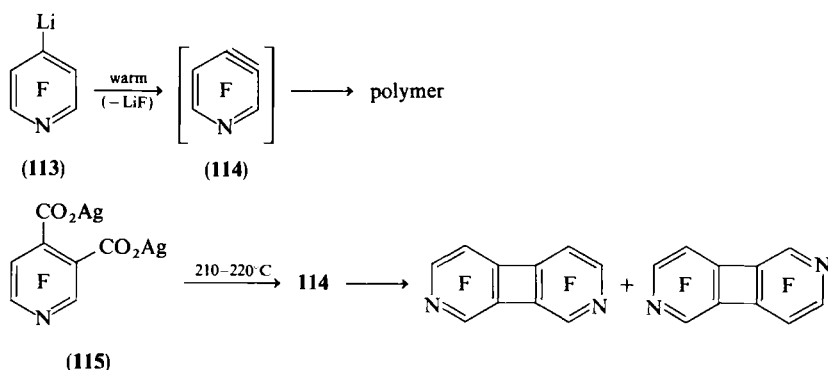
³⁵⁴ G. G. Furin and G. G. Yakobson, *Izv. Sib. Otd. Akad. Nauk SSSR, Ser. Khim. Nauk*, 128 (1972) [*CA* **78**, 72263 (1973)].

³⁵⁵ R. D. Chambers, W. K. R. Musgrave, and P. J. Urben, unpublished results.

³⁵⁶ R. V. Grigorash, V. V. Lyalin, L. A. Alekseeva, and L. M. Yagupol'ski, *Zh. Org. Khim.* **14**, 2623 (1978) [*CA* **90**, 137590 (1979)].

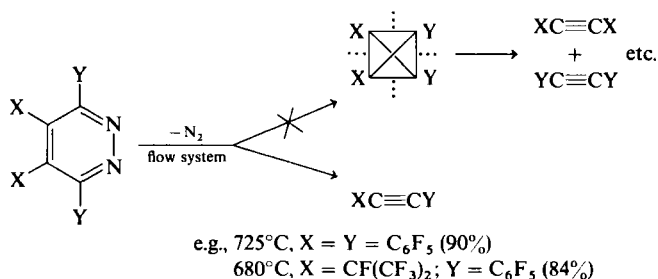
2. Arynes

Aryne formation by elimination of lithium fluoride limits the stability of **113**; a polymer is formed, but attempts to trap the aryne (**114**) were unsuccessful.³⁵² Decarboxylation of metal salts of tetrafluoroisonicotinic acid occurs,³⁵⁷ giving the corresponding metal derivative, but pyrolysis of the disilver salt (**115**) appears to produce the aryne (**114**), since small amounts of diazabiphenylenes may be isolated from the reaction product.^{358,359}



G. FRAGMENTATION AND REARRANGEMENT PROCESSES

Attempts to eliminate nitrogen from fluorinated pyridazines and related compounds were made originally with a view to the generation of cyclobutadienes or even tetrahedranes as intermediates. Elimination does occur

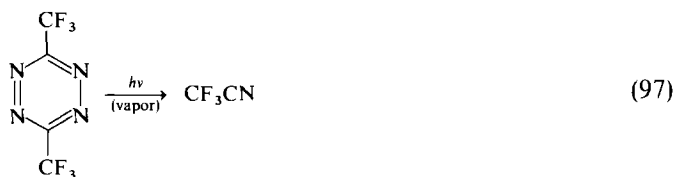
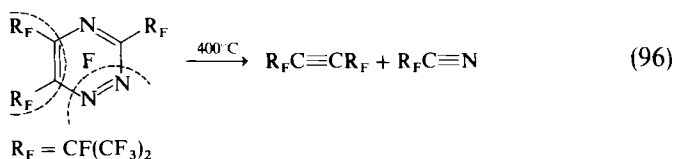


SCHEME 33

³⁵⁷ P. Sartori and H. Adelt, *J. Fluorine Chem.* **3**, 275 (1973).

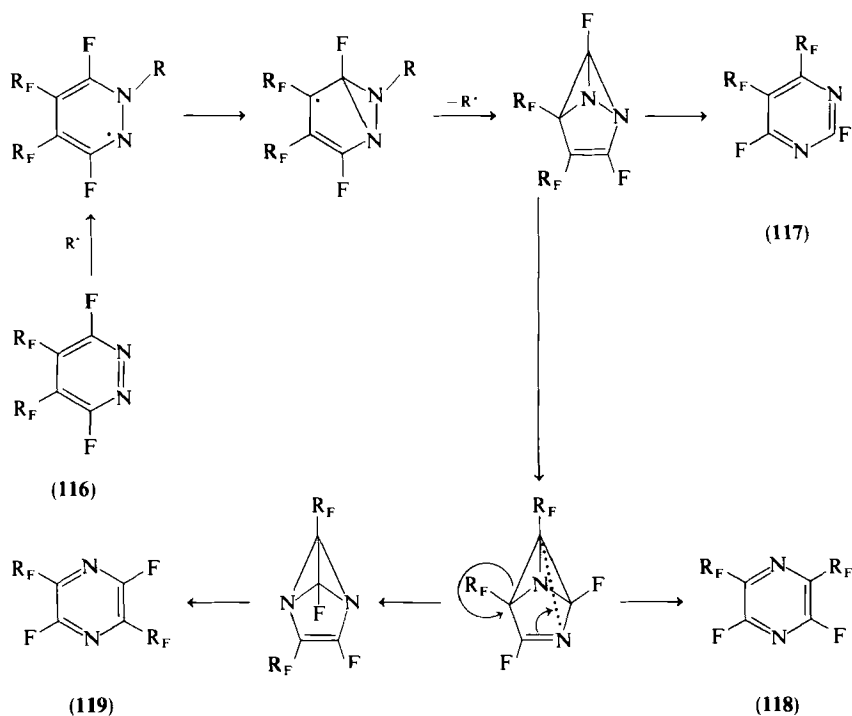
³⁵⁸ E. G. Bartsch, A. Golloch, and P. Sartori, *Chem. Ber.* **105**, 3463 (1972).

³⁵⁹ G. Haegle, P. Sartori, and A. Golloch, *Z. Naturforsch., Teil B* **28**, 758 (1973).



in some cases (Scheme 33,³⁶⁰ Eqs. 96³¹² and 97¹²⁵), but there is no indication of cyclic intermediates from the fluorinated compounds.

More frequently, thermal reactions of fluorinated pyridazines (116) lead to pyrimidines (117) together with, in some cases, small amounts of pyrazine



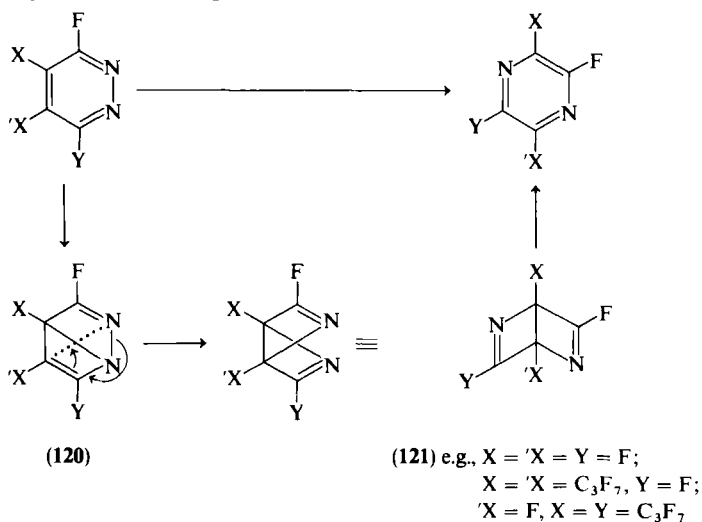
SCHEME 34

³⁶⁰ R. D. Chambers, M. Clark, J. A. H. MacBride, W. K. R. Musgrave, and K. C. Srivastava, *J. C. S. Perkin I*, 125 (1974).

derivatives (**118** or **119**).³⁶¹⁻³⁶⁴ These reactions proceed in surprisingly high yields but elucidation of the mechanism has posed many problems, not least of which is the recent discovery³⁶⁴ that the presence of one compound may promote rearrangement of the other. It is now believed³⁶⁵ that this effect is a highly efficient process promoted by radicals, possibly as indicated in Scheme 34.

Valence Isomers

A process for the rearrangement of fluorinated pyridazines, promoted by ultraviolet radiation, has now been elucidated^{366,377} and may be summarized as in Scheme 35. Each intermediate stage, i.e., the valence isomers **120** and **121**, in this fascinating process has been isolated and characterized before further conversion. Conversion of perfluoro-3,6-dimethylpyridazine to a pyrazine has been described¹²⁵ and some 1,2-shifts are also observed on ultraviolet irradiation.^{42,312,366} Ring opening of 2-trifluoromethylquinoline to the corresponding 3,1-benzoxazepine occurs on irradiation.³⁶⁸



SCHEME 35

³⁶¹ R. D. Chambers, J. A. H. MacBride, and W. K. R. Musgrave, *J. Chem. Soc. C*, 3384 (1971).

³⁶² R. D. Chambers, M. Clark, J. R. Maslakiewicz, W. K. R. Musgrave, and P. G. Urben, *J. C. S. Perkin I*, 1513 (1974).

³⁶³ R. D. Chambers, C. R. Sargent, and M. Clark, *J. C. S. Chem. Commun.*, 445 (1979).

³⁶⁴ R. D. Chambers and C. R. Sargent, *J. C. S. Chem. Commun.*, 446 (1979).

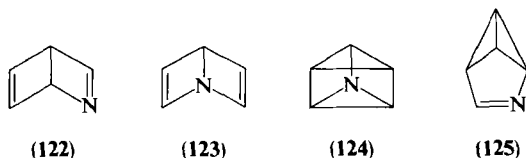
³⁶⁵ R. D. Chambers and C. R. Sargent, unpublished results.

³⁶⁶ R. D. Chambers, J. A. H. MacBride, J. R. Maslakiewicz, and K. C. Srivastava, *J. C. S. Perkin I*, 396 (1975).

³⁶⁷ R. D. Chambers, J. R. Maslakiewicz, and K. C. Srivastava, *J. C. S. Perkin I*, 1130 (1975).

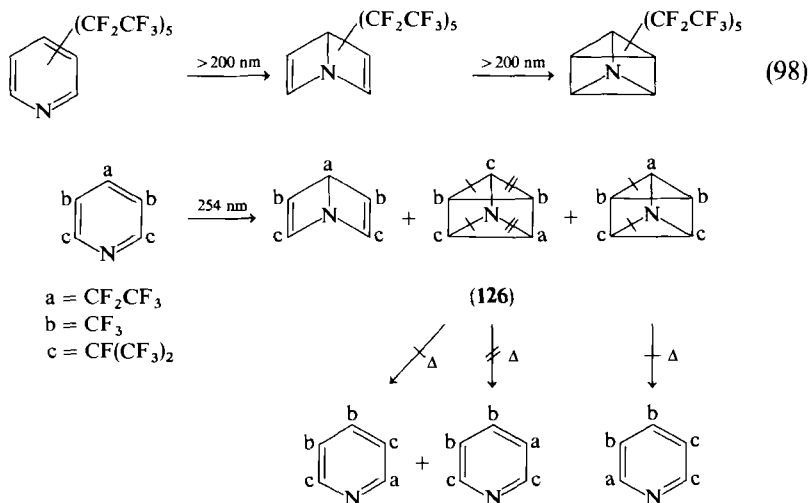
³⁶⁸ C. Kaneko, S. Hayashi, and Y. Kobayashi, *Chem. Pharm. Bull.* **22**, 2147 (1974).

Isomers **120** and **121** appear to be the only valence isomers of aromatic diazines described, and they are surprisingly stable. Even more spectacular, however, are the stabilities of valence isomers of fluorinated pyridines corresponding to structures **122**–**124**. So far however, an azabenzvalene derivative (e.g., **125**) has not been described. Pyridine itself forms a valence isomer that



has structure **122**,³⁶⁹ and this is what might be expected on the basis of simple bond energy summation. A more sophisticated approach leads to the same conclusion.³⁷⁰ In systems with five perfluoroalkyl groups, only the isomer corresponding to **123** is obtained, together with azaprismanes (Eq. 98,³¹³ Scheme 36³⁷¹), and the formation of azaprismane **126** has been attributed to a 1,3-shift process similar to that discussed earlier for pyridazines.

Compound **127**, containing only two perfluoroalkyl groups, also gives a product corresponding to **123**.^{372,373} Presumably, buttressing of groups is



SCHEME 36

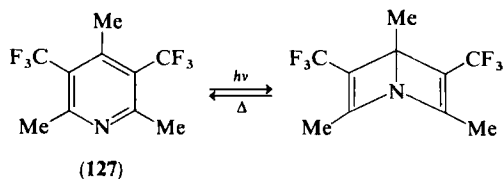
³⁶⁹ K. E. Wilzbach and D. J. Rausch, *J. Am. Chem. Soc.* **92**, 2178 (1970).

³⁷⁰ M. J. S. Dewar, G. P. Ford, J. P. Ritchie, and H. S. Rzepa, *J. Chem. Res. (S)*, 26 (1978).

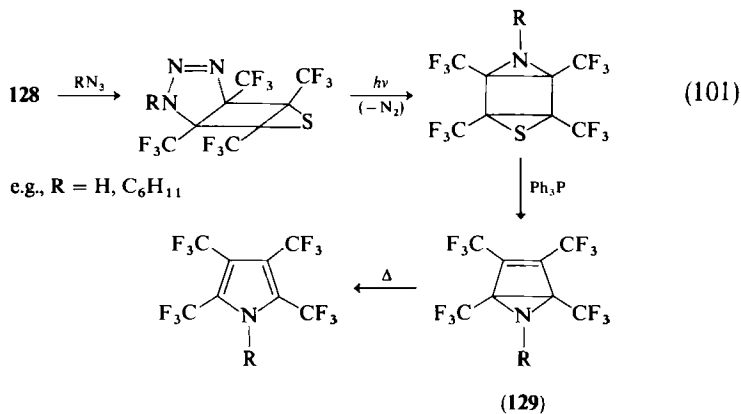
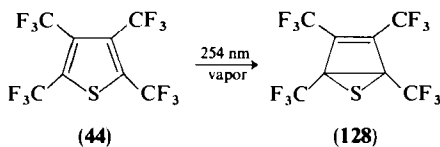
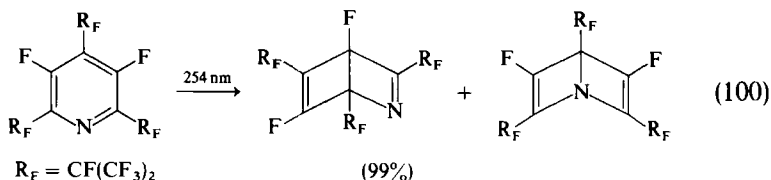
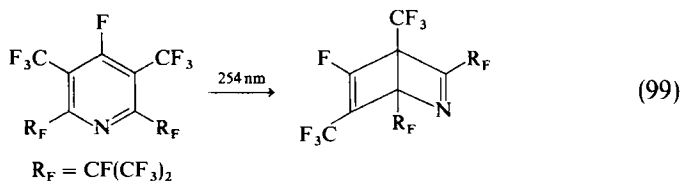
³⁷¹ R. D. Chambers and R. Middleton, *J. C. S. Perkin I*, 1500 (1977).

³⁷² Y. Kobayashi, A. Ohsawa, M. Baba, T. Sato, and I. Kumadaki, *Chem. Pharm. Bull.* **24**, 2219 (1976) [*CA* **86**, 89545 (1977)].

³⁷³ Y. Kobayashi and A. Ohsawa, *Chem. Pharm. Bull.* **24**, 2225 (1976) [*CA* **86**, 105577 (1977)].



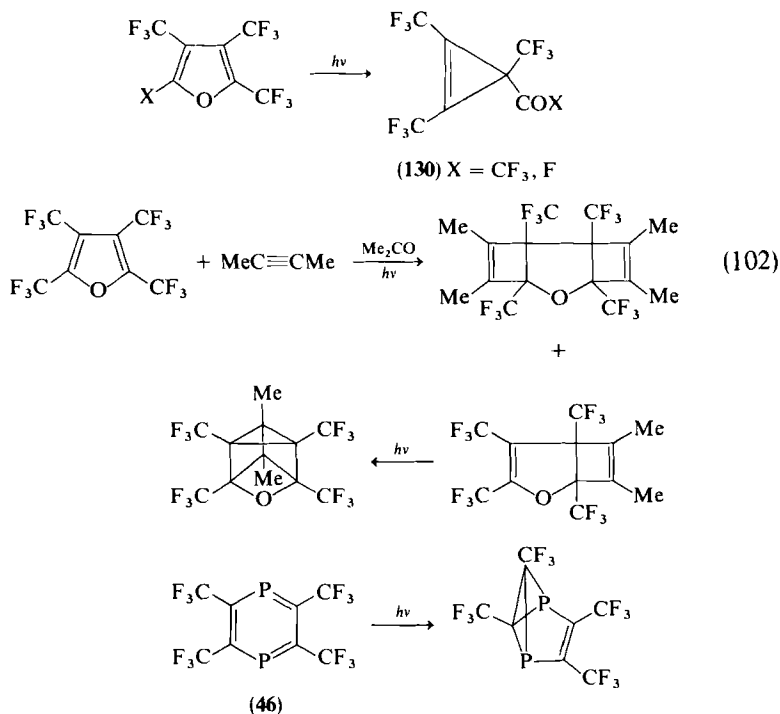
still high in this system, but pyridine derivatives containing three or four perfluoroalkyl groups gave the first very stable valence isomers corresponding to structure 122 (Eqs. 99, 100).³⁷⁴



³⁷⁴ R. D. Chambers and R. Middleton, *J. C. S. Chem. Commun.*, 154 (1977).

A valence isomer is obtained in the photolysis of the thiophene derivative **44**, which was subsequently shown to have the structure **128**.³⁷⁵⁻³⁷⁸ The isomer **128** has been converted to a valence isomer (**129**) of the corresponding pyrrole by a novel sequence starting with the appropriate azide (Eq. 101).^{379,380}

Irradiation of fluorinated furans did not give the valence isomers but, instead, the more familiar ring opening to cyclopropenylketones (**130**).²⁹⁸ In the presence of alkynes, however, a novel series of $(2\pi + 2\pi)$ -cycloadditions occurs (Eq. 102).³⁸¹ An analog of benzvalene has been obtained from the diphosphabenzene (**46**).¹²⁹



³⁷⁵ H. A. Wiebe, S. Bradlavsky, and J. Heicklen, *Can. J. Chem.* **50**, 2721 (1972).

³⁷⁶ Y. Kobayashi, I. Kumadaki, A. Ohsawa, and Y. Sekine, *Tetrahedron Lett.*, 2841 (1974).

³⁷⁷ Y. Kobayashi, I. Kumadaki, A. Ohsawa, Y. Sekine, and H. Mochizuki, *Chem. Pharm. Bull.* **23**, 2773 (1975) [*CA* **84**, 135384 (1976)].

³⁷⁸ Y. Kobayashi, I. Kumadaki, and A. Ohsawa, *Heterocycles* **6**, 1587 (1977) [*CA* **88**, 136394 (1978)].

³⁷⁹ Y. Kobayashi, I. Kumadaki, A. Ohsawa, and A. Ando, *J. Am. Chem. Soc.* **99**, 7350 (1977).

³⁸⁰ Y. Kobayashi, A. Ando, and I. Kumadaki, *J. C. S. Chem. Commun.*, 509 (1978).

³⁸¹ Y. Kobayashi and Y. Hanzawa, *Tetrahedron Lett.* **44**, 4301 (1978).

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1,2- and 2,1-Benzothiazines and Related Compounds

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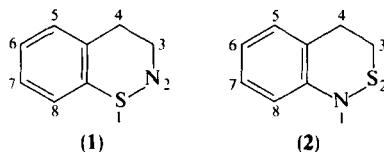
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I. Introduction

In recent years there has been a dramatic increase in the number of literature references to 1,2-benzothiazines (**1**) and 2,1-benzothiazines (**2**). Prior to 1956, the only reference was that published in 1923 by von Braun.¹ In the last 15 years, however, many publications have presented interesting chemistry and important applications. Much of the literature deals with anti-inflammatory 1,2-benzothiazines ("oxicams") such as piroxicam. The

¹ J. von Braun, *Ber. Dtsch. Chem. Ges.* **56**, 2332 (1923).

only prior review of these compounds, by Prota² for the period from 1972 to early 1974, reported six references to 1,2-benzothiazines.



The present review comprehensively surveys the literature up to July 1979, utilizing *Chemical Abstracts Chemical Substance Indexes*, through volume **90** (January–June, 1979), as well as the computer-based *CA Condensates/CASIA* and the *Derwent World Patents Index* data retrieval services. The focus of this survey is primarily on the two ring systems **1** and **2** and their oxidized derivatives. A few related ring systems, such as dibenzo- and hetero ring-fused 1,2-thiazines are included where it appeared appropriate to do so because of similar chemistry or analogous utility to the benzothiazine compounds. This chapter will bring together all of the literature references to the title compounds, discuss the routes employed for their synthesis, and describe their reported chemical transformations. Spectral data and utility are also discussed.

Because of the commercial importance of some of these compounds, a significant number of references appear in the patent literature. Wherever possible, foreign patents have been traced to a United States basic patent. Where this was not possible, the foreign patent and *Chemical Abstracts* citations are given. Patents found to be equivalent to one another are grouped under a single reference number.

II. 1,2-Benzothiazines

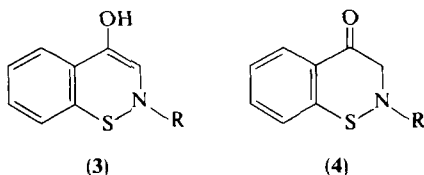
A. SYNTHESSES

1. 1,2-Benzothiazin-4-ones

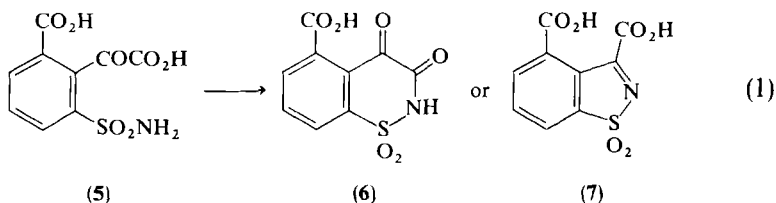
This group represents by far the largest class of 1,2-benzothiazines. Since many of these compounds are capable of keto–enol tautomerism, the 4-hydroxy-1,2-benzothiazines (**3**) as well as the 1,2-benzothiazin-4-ones (**4**) will be grouped in this section. Where the enol form has been demonstrated by spectral evidence, these compounds will be named as 4-hydroxy deriva-

² G. Prota, in "Organic Compounds of Sulphur, Selenium and Tellurium" (D. H. Reid, ed.), Vol. 3, p. 708. The Chemical Society. London (1975).

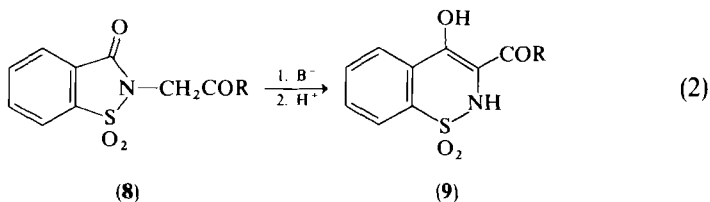
tives rather than 1,2-benzothiazin-4-ones. This is in keeping with the practice of the most recent volumes of *Chemical Abstracts Chemical Substances Index*.



The earliest report of a 1,2-benzothiazin-4-one is that of von Braun.¹ Cyclodehydration of carboxylic acid **5** produced, according to elemental analysis, a material assigned the structure of a 1,2-benzothiazine-3,4-dione (**6**) (Eq. 1). Since no additional proof for the structure of **6** was provided,¹ the isomeric benzisothiazole dicarboxylic acid (**7**) cannot be excluded.



A versatile synthetic approach to 4-hydroxy-1,2-benzothiazines was discovered by Abe and co-workers³: 2-phenacyl-1,2-benzisothiazolin-3-ones (**8**; R = Ar) with strong base produce 3-benzoyl-4-hydroxy-2*H*-1,2-benzothiazine 1,1-dioxides (**9**; R = Ar) (Eq. 2). Yields up to 93% could be obtained using sodium ethoxide in ethanol.



Methylation of compound **9** occurs on the sulfonamide nitrogen.³ Although compound **9** was named as a 1,2-benzothiazin-4-one, infrared spectral data obtained by these workers,³ as well as later work by others, strongly support a 4-hydroxy tautomeric form.

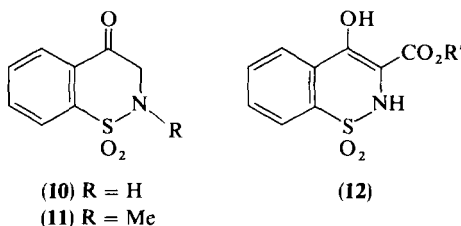
The findings of Abe *et al.*³ were later extended by Zinnes and co-workers⁴ in a series of publications dealing with 1,2-benzothiazines. For example,

³ K. Abe, S. Yamamoto, and K. Matsui, *J. Pharm. Soc. Jpn.* **76**, 1058 (1956) [*CA* **51**, 3499 (1957)].

⁴ H. Zinnes, R. A. Comes, F. R. Zuleski, A. N. Caro, and J. Shavel, *J. Org. Chem.* **30**, 2241 (1965).

2-acetyl-1,2-benzisothiazolin-3-one (**8**; R = Me) was converted by two equivalents of sodium ethoxide to 3-acetyl-4-hydroxy-2*H*-1,2-benzothiazine 1,1-dioxide (**9**; R = Me). Evidence was presented to support an initial ethanolysis of compound **8** (R = Me) by one equivalent of sodium ethoxide, followed by cyclization of the intermediate ester. This ring-expansion reaction has been reviewed.⁵ Spectral evidence clearly supports the enol form for compound **9** (R = Me).

Unexpectedly, the 3-acetyl compound was deacetylated when heated in benzene with ethylene glycol in the presence of an acid.⁶ The 4-ketal produced was then readily cleaved by dilute hydrochloric acid to give 3,4-dihydro-2*H*-1,2-benzothiazin-4-one 1,1-dioxide (**10**). As expected, *N*-methylation of compound **10** produced 2-methyl-3,4-dihydro-2*H*-1,2-benzothiazin-4-one 1,1-dioxide (**11**).



The benzisothiazoline ester **8** (R = OR') is isomerized to a 1,2-benzothiazine-3-carboxylic ester (**12**) by sodium ethoxide in ethanol^{7,8} or by sodium methoxide in dimethyl sulfoxide.⁹ This rearrangement appears to be more sensitive to reaction conditions and solvent than the rearrangement of 2-phenacyl-1,2-benzisothiazolin-3-ones such as **8** (R = Ar) (Eq. 2), and two laboratories^{8,9} report unsatisfactory attempts to rearrange compound **8** (R = OMe) to **12** (R' = Me) with sodium methoxide in methanol.

Another synthetic route to 1,2-benzothiazin-4-one 1,1-dioxides produced 13–19% of compound **11** when *o*-diazoacetylbenzenesulfonamide (**13**; R = Me) was cyclized by formic acid in acetonitrile¹⁰ (Eq. 3). A carbene was suggested as an intermediate in this transformation.¹⁰ Much better yields (43–70%) of the corresponding *N*-phenyl compound (**14**) were obtained when the corresponding *N*-phenylsulfonamide (**13**; R = Ph) was cyclized.¹⁰

⁵ H. Hettler, *Adv. Heterocycl. Chem.* **15**, 259 (1973).

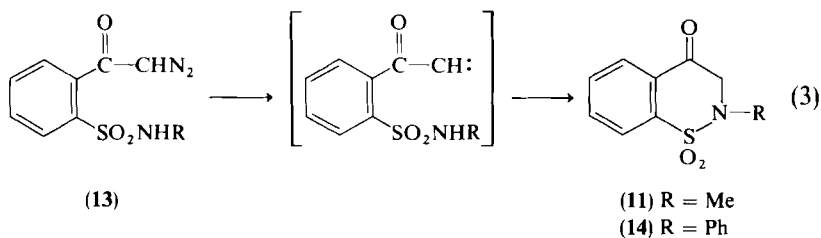
⁶ H. Zinnes, R. A. Comes, and J. Shavel, *J. Org. Chem.* **31**, 162 (1966).

⁷ C. R. Rasmussen, U.S. Patent 3,501,466 (1970) [*CA* **72**, 121562 (1970)].

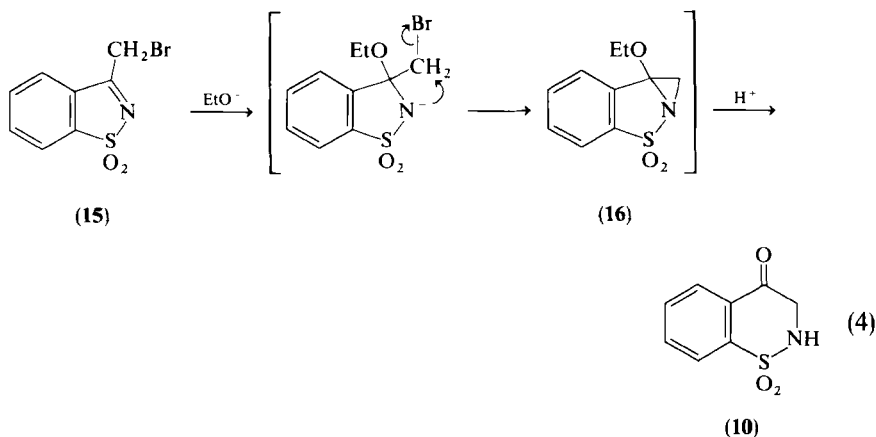
⁸ C. R. Rasmussen, *J. Org. Chem.* **39**, 1554 (1974).

⁹ J. G. Lombardino, E. H. Wiseman, and W. McLamore, *J. Med. Chem.* **14**, 1171 (1971).

¹⁰ G. Heyes, G. Holt, and A. Lewis, *J. C. S., Perkin I*, 2351 (1972).



Ring expansion of 3-bromomethyl-1,2-benzisothiazole 1,1-dioxide (**15**) by sodium ethoxide produced 3,4-dihydro-2*H*-1,2-benzothiazin-4-one (**10**) in 66% yield.¹¹ The favored mechanism involves a three-membered cyclic intermediate (**16**) opened by ethoxide attack on the ether portion of **16** (Eq. 4).¹¹ This synthetic route would appear to be preferred for preparing the ketone **10**.

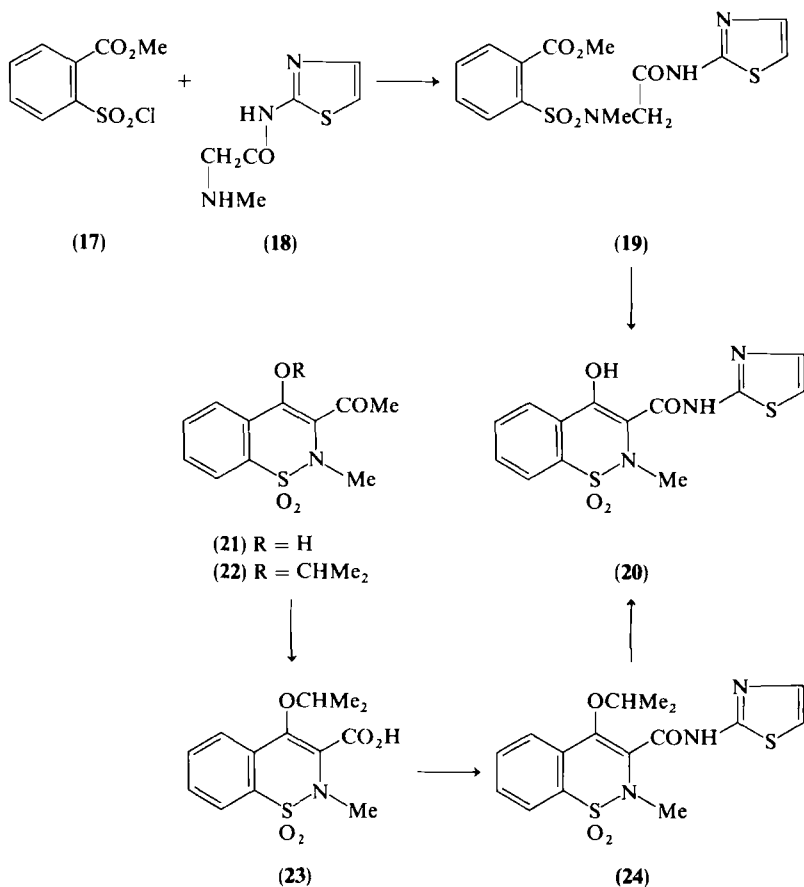


Two additional routes gave low yields¹² of 1,2-benzothiazine-3-carboxamide **20** (sudoxicam). Thus, *N*-carbobenzyloxysarcosine was converted to the sarcosine amide **18**. Formation of sulfonamide **19** using the sulfonyl chloride **17** followed by cyclization produced the 3-carboxamide **20** (Scheme 1).

In another approach, protection of **21** via formation of the enol ether **22** allowed oxidation of the acetyl derivative **22** to carboxylic acid **23**. Amide formation followed by hydrolysis of the enol ether **24** yielded compound **20** (Scheme 1).¹²

¹¹ R. A. Abramovitch, K. M. More, I. Shinkai, and P. C. Srinivasan, *J. C. S., Chem. Commun.*, 771 (1976).

¹² J. G. Lombardino and H. A. Watson, *J. Heterocycl. Chem.* **13**, 333 (1976).



SCHEME 1

A number of sulfamoyl-substituted 3-acyl-4-hydroxy-1,2-benzothiazine 1,1-dioxides were prepared¹³ by base-catalyzed isomerization of sulfamoyl derivatives of benzisothiazolin-3-ones by essentially the method of Abe (Eq. 2).

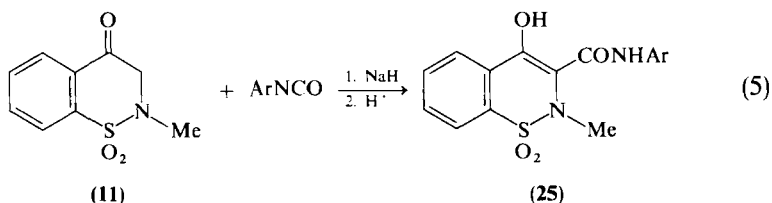
Interest in the 4-hydroxy-2H-1,2-benzothiazine 1,1-dioxides was significantly increased by the discovery by Lombardino and co-workers^{9,14,15} of

¹³ A. Kraaijeveld and A. M. Akkerman, U.S. Patent 3,284,450 (1966) [CA 66, 28789 (1967)]; Netherlands Patent Appl. 283,525 [CA 62, 16262 (1965)].

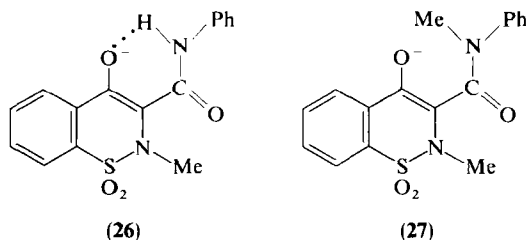
¹⁴ J. G. Lombardino, U.S. Patent 3,591,584 (1971) [CA 73, 120647 (1970) for equivalent German Patent 1,943,265].

¹⁵ J. G. Lombardino, in "Antiinflammatory Agents: Chemistry and Pharmacology" (R. A. Scherrer and M. W. Whitehouse, eds.), Vol. 1, p. 129. Academic Press, New York, 1974.

potent anti-inflammatory activity in 3-carboxamides of 4-hydroxy-2*H*-1,2-benzothiazine 1,1-dioxides (**25**). Synthesis of carboxamides such as **25** has been approached by several routes. Thus, compound **11**, although unstable under some basic conditions,⁶ combines with isocyanates in the presence of sodium hydride in dimethylformamide to produce the desired carboxamides **25** (Eq. 5).⁹



Of the many reported analogs of compound **25**, the carboxanilide (Ar = Ph) has been most thoroughly studied.⁹ Its unusual acidity ($\text{p}K_a'$ 7.3) was explained by a stabilized, hydrogen-bonded form of the enolate (**26**). The *N*-methyl-*N*-phenylcarboxamide (**27**), which lacks an amide proton for stabilizing the enolate, exhibits⁹ $\text{p}K_a'$ 9.8. Other examples of compounds made by the isocyanate method shown in Eq. (5) have been reported.^{16,17}



Another useful synthetic route to amides **25** utilized the methyl ester (**12**; R' = Me) prepared by ring expansion of the corresponding benzisothiazoline ester **8** (R = OMe).⁹ Methylation of **12** produced ester **28**. Combination of various amines with ester **28**, or the corresponding ethyl ester, gives analogs of compound **25**.^{7,8,17,18} The use of heterocyclic amines in this reaction has produced the *N*-heterocyclic amides sudoxicam (**20**)¹⁹ and piroxicam (**29**),^{20,21} potent anti-inflammatory agents that are discussed more fully in Section II,D.

¹⁶ H. Zinnes, N. A. Lindo, and J. Shavel, U.S. Patent 3,646,021 (1972) [*CA* 77, 5499 (1972)].

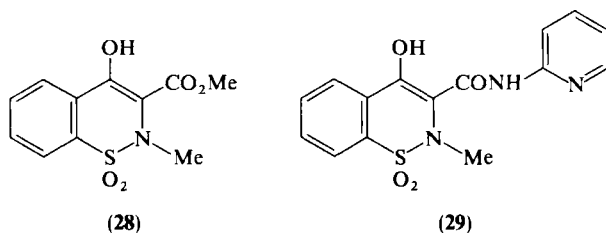
¹⁷ H. Zinnes, N. A. Lindo, J. C. Sircar, M. L. Schwartz, and J. Shavel, *J. Med. Chem.* 16, 44 (1973).

¹⁸ J. G. Lombardino, *Org. Prep. Proced. Int.* 12, 269 (1980).

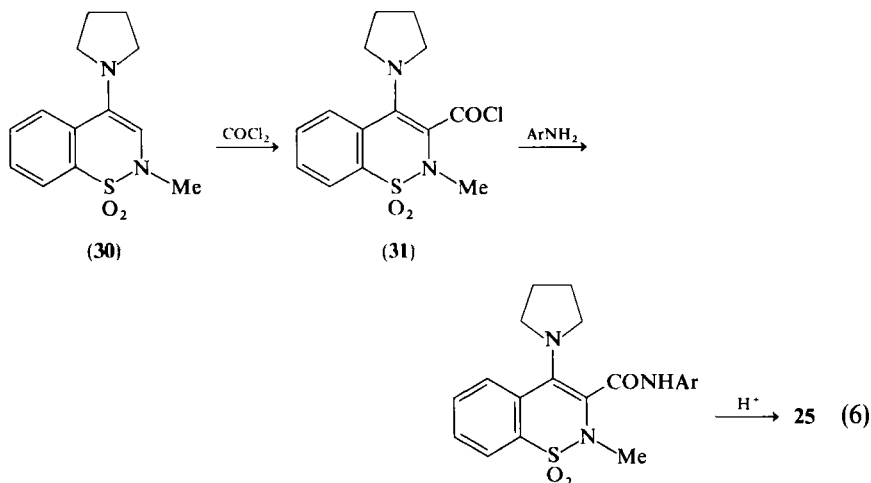
¹⁹ J. G. Lombardino and E. H. Wiseman, *J. Med. Chem.* 15, 848 (1972).

²⁰ E. H. Wiseman, Y.-H. Chang, and J. G. Lombardino, *Arzneim.-Forsch.* 26, 1300 (1976).

²¹ J. G. Lombardino, E. H. Wiseman, and J. Chiaini, *J. Med. Chem.* 16, 493 (1973).



An enamine derivative (30) prepared from compound 11 can be acylated with phosgene and the resulting acid chloride (31) then converted to the desired amides **25** (Eq. 6).^{17,22,23} This sequence of reactions also proved useful for preparing 3-aminoalkyl esters and 3-aminoalkylamides related to **25**.²⁴



Many patents cover synthetic routes to anti-inflammatory compounds such as **20**, **25**, or **29**. The transformations shown in Scheme 1 are included in process patents.²⁵⁻²⁹ Transamidation of certain 3-carboxanilides (**32**) produces novel N-substituted carboxamides of 4-hydroxy-2H-1,2-benzothiazine 1,1-dioxides (**25**) (Eq. 7).³⁰

²² J. C. Sircar, H. Zinnes, and J. Shavel, U. S. Patent 3,821,211 (1974) [see *CA* **79**, 146531 (1973) for equivalent German Patent 2,308,305; *CA* **82**, 73007 (1975) for German Patent 2,365,436].

²³ J. C. Sircar, H. Zinnes, and J. Shavel, U.S. Patent 3,808,205 (1974) [*CA* **81**, 13538 (1974)].

²⁴ H. Zinnes, J. Sircar, and J. Shavel, U.S. Patent 3,856,784 (1974) [*CA* **82**, 140158 (1975)].

²⁵ J. G. Lombardino, U.S. Patent 3,853,862 (1974) [*CA* **82**, 112092 (1975)].

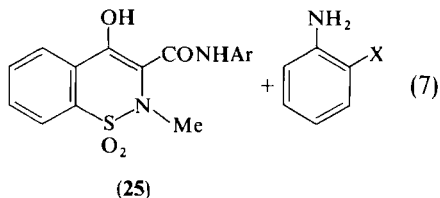
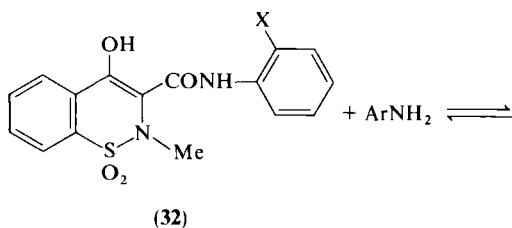
²⁶ J. G. Lombardino, U.S. Patent 3,927,002 (1975) [*CA* **84**, 135693 (1976)].

²⁷ J. G. Lombardino, U.S. Patent 3,954,786 (1976) [*CA* **85**, 46723 (1976)].

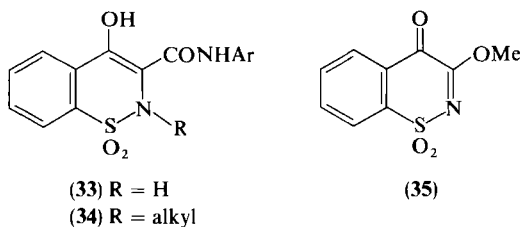
²⁸ J. G. Lombardino, U.S. Patent 3,971,802 (1976) [*CA* **86**, 5478 (1977)].

²⁹ J. G. Lombardino, U.S. Patent 3,892,740 (1975) [*CA* **83**, 164213 (1975)].

³⁰ J. G. Lombardino, U.S. Patent 3,891,637 (1975) [*CA* **83**, 179077 (1975)].



When amides such as **33**, unsubstituted on the sulfonamide nitrogen atom, are treated with base and an alkylating agent, alkylation takes place preferentially on the sulfonamide nitrogen to yield **34**.³¹



Oxidation of 3-acyl-4-hydroxy-2H-1,2-benzothiazine 1,1-dioxide (**9**) in methanol by silver carbonate or *tert*-butyl hypochlorite produced 3-methoxy-4H-1,2-benzothiazin-4-one 1,1-dioxide (**35**),³² apparently by a free radical mechanism with participation of solvent.

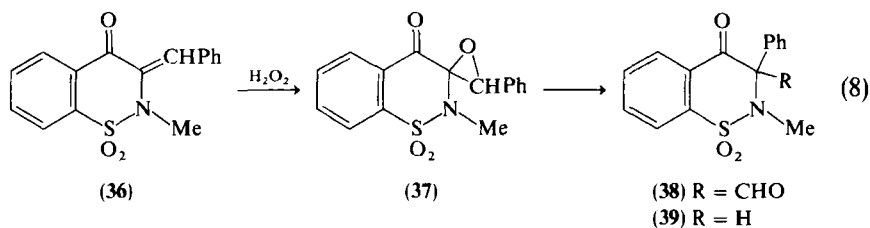
The multistep preparation of 3-phenyl-4-hydroxy-2H-1,2-benzothiazine 1,1-dioxide (**39**) led from 3-benzylidene-2-methyl-2H-1,2-benzothiazin-4-one 1,1-dioxide (**36**) to an epoxide (**37**) isomerized by boron trifluoride into the 3-formyl compound **38**. Acid-catalyzed deformylation of **38** yielded **39** (Eq. 8).^{33,34} This reaction provided access to 3-aryl-1,2-benzothiazines from readily available 3-benzylidene-1,2-benzothiazines (see Section II,B,1).

³¹ J. G. Lombardino, Netherlands Patent 7,614,135 (1977) [CA **88**, 121216 (1978)].

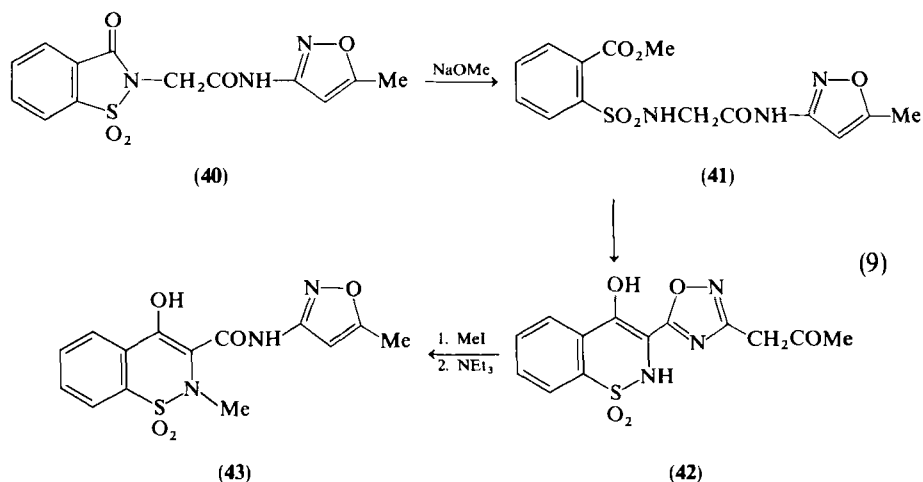
³² H. Zinnes J. Shavel, and M. S. Sternberg, U.S. Patent 3,479,436 (1969) [CA **72**, 55476 (1970)]; U.S. Patent 3,492,296 (1970) [CA **72**, 90487 (1970)].

³³ H. Zinnes and J. Shavel, U.S. Patent 3,692,780 (1972) [CA **77**, 152202 (1972)].

³⁴ H. Zinnes and J. Shavel, *J. Heterocycl. Chem.* **10**, 95 (1973).



An interesting rearrangement was observed^{35,36} during the preparation of 4-hydroxy-*N*-(5-methyl-3-isoxazolyl)-2-methyl-2*H*-1,2-benzothiazine-3-carboxamide 1,1-dioxide (43) (Eq. 9). Sodium methoxide cleaved the benzisothiazoline derivative 40 to the expected benzoate ester 41, but this was cyclized by base to a 4-hydroxy-2*H*-1,2-benzothiazine (42) with simultaneous conversion of the isoxazole moiety to an oxadiazole. Compound 42 was *N*-methylated by methyl iodide and the product converted to the desired amide 43 by treatment with triethylamine in xylene, a process which simultaneously reconverts the oxadiazole side chain to an isoxazole.

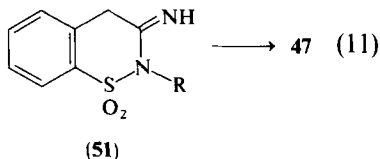
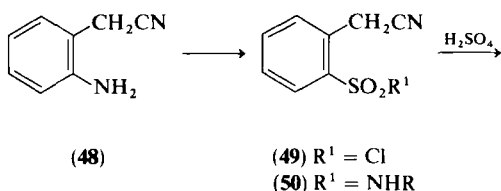


Direct rearrangement of benzisothiazoline amides, such as compound 8 (R = NHPh), to the 1,2-benzothiazine-3-carboxamide 44 has been accomplished³⁷ in dimethyl sulfoxide using sodium methoxide.

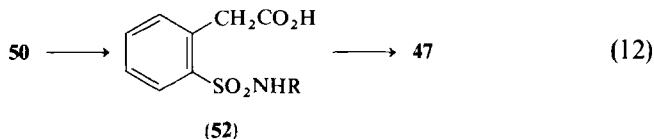
³⁵ A. C. Fabian, J. D. Genzer, C. F. Kasulanis, J. Shavel, and H. Zinnes, U.S. Patent 3,987,038 (1976) [CA 86, 72679 (1977)]; U.S. Patent 4,076,722 (1978) [CA 86, 72679 (1977)].

³⁶ A. C. Fabian, J. D. Genzer, C. F. Kasulanis, J. Shavel, and H. Zinnes, U.S. Patent 3,957,772 (1976) [CA 85, 46725 (1976)]; U.S. Patent 4,041,042 (1977) [CA 87, 168068 (1977)]; U.S. Patent 4,022,796 (1977) [CA 87, 39523 (1977)]; U.S. Patent 4,018,762 (1977) [CA 87, 53345 (1977)]; U.S. Patent 3,978,073 (1976) [CA 86, 16690 (1977)].

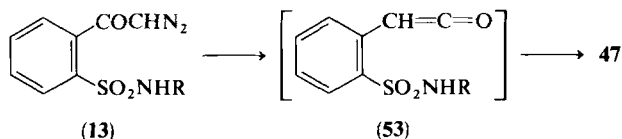
³⁷ H. Zinnes, N. A. Lindo, and J. Shavel, U.S. Patent 4,074,048 (1978) [CA 88, 190868 (1978)]; U.S. Patent 4,116,964 (1978).



Another synthetic approach to **47** utilized 2-cyanomethylbenzenesulfonyl chloride (**49**) for the preparation in two steps of 2-sulfonamidophenylacetic acids (**52**) which were cyclodehydrated by acetic anhydride/sodium acetate to **47** (Eq. 12).⁴¹ Examples of the R substituent in **47** prepared by this method include *n*-propyl, isopropyl, *n*-butyl, allyl, propargyl, chlorophenyl, and morpholinoethyl.⁴¹



Photolysis of the *o*-diazoacetylbenzenesulfonamide **13** (R = Me) over seven days gives a reasonable yield of **47** (R = Me),¹⁰ presumably via the Wolff rearrangement of the diazoketone to a ketene intermediate (**53**). Heating **13** (R = Ph) in refluxing chlorobenzene gave only 30% of **47** (R = Ph).¹⁰

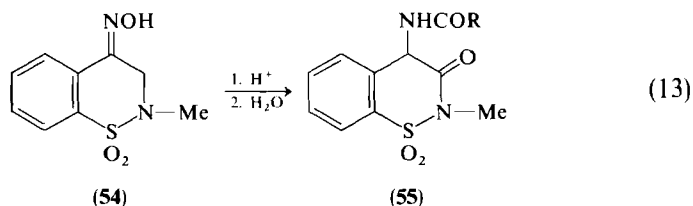


Zinnes and co-workers⁴² report an interesting Semmler-Wolff transformation of the oxime **54** (Eq. 13) by trifluoroacetic acid or acetic acid/BF₃ to the corresponding 1,2-benzothiazin-3(2*H*)-one 1,1-dioxides (**55**) (Eq. 13).

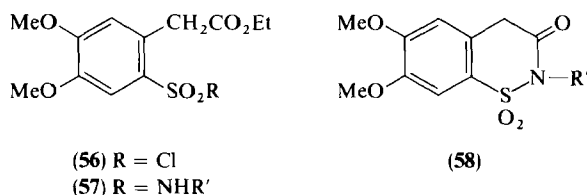
Catsoulacos has synthesized 2-substituted 3,4-dihydro-6,7-dimethoxy-1,2-benzothiazin-3(2*H*)-one 1,1-dioxides (**58**): chlorosulfonation of 3,4-

⁴¹ E. Sianesi, R. Redaelli, M. J. Magistretti, and E. Massarani, *J. Med. Chem.* **16**, 1133 (1973).

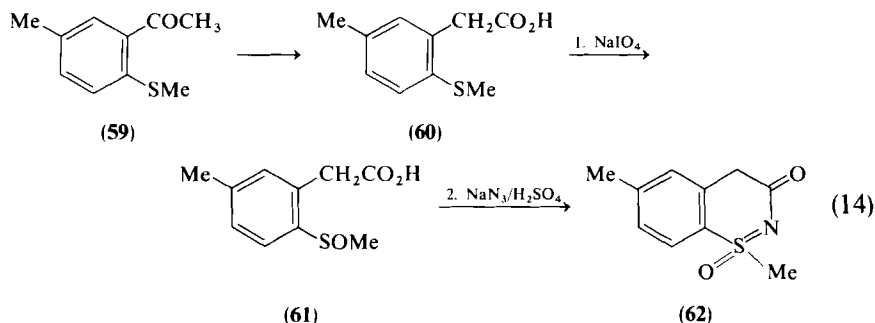
⁴² H. Zinnes, R. A. Comes, and J. Shavel, *J. Heterocycl. Chem.* **14**, 1063 (1977).



dimethoxyphenylacetic ester gave the sulfonyl chloride (**56**), which was converted into the sulfonamide (**57**) and cyclodehydrated using phosphorus pentachloride or heat to **58** ($R' = \text{H}$, methyl, isopropyl, phenyl, and *p*-tolyl).^{43,44} The same reactions gave **58** ($R = 5\text{-chloro-2-pyridyl}$)⁴⁵ or **58** ($R = \text{methyl-2-pyridyl}$).⁴⁶



Williams and Cram⁴⁷ prepared the cyclic sulfoximide **62**, with a chiral sulfur atom, in three steps from 2-methylthio-5-methylacetophenone (**59**). The latter compound was converted into a 2-methylthiophenylacetic acid derivative (**60**), which was then oxidized to the 2-methylsulfinyl compound **61**. Compound **61** was cyclized to **62** in 60% yield using sodium azide in sulfuric acid (Eq. 14).⁴⁸



⁴³ P. Catsoulacos, *J. Heterocycl. Chem.* **8**, 947 (1971).

⁴⁴ P. Catsoulacos and C. Camoutsis, *J. Chem. Eng. Data* **22**, 353 (1977).

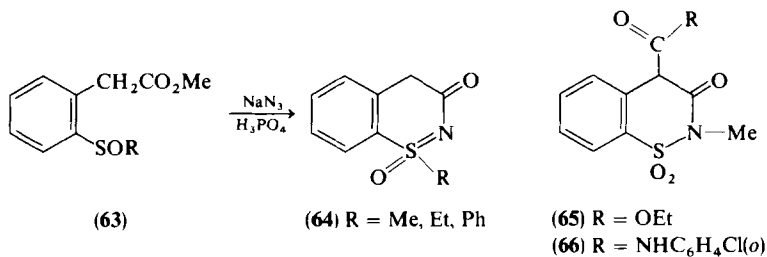
⁴⁵ P. Catsoulacos, *Chim. Ther.* **7**, 243 (1972).

⁴⁶ P. Catsoulacos, *Chem. Chron.* **3**, 129 (1974) [*CA* **84**, 43960 (1976)].

⁴⁷ T. R. Williams and D. J. Cram, *J. Am. Chem. Soc.*, **93**, 7333 (1971).

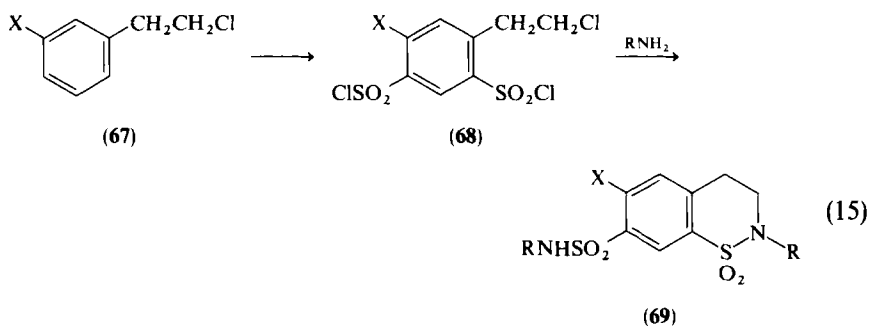
⁴⁸ T. R. Williams and D. J. Cram, *J. Org. Chem.* **38**, 20 (1973).

Stoss and Satzinger⁴⁹⁻⁵¹ utilized similar methodology (sodium azide in polyphosphoric acid/ P_2O_5) to prepare examples of **64** from the corresponding 2-alkylsulfinylphenylacetic esters **63**. The 4-carboethoxy derivative **65** was prepared by ethanolysis of the *o*-chlorocarboxanilide **66**.³⁸



3. Other 1,2-Benzothiazines

A few reports have appeared of syntheses of 1,2-benzothiazines lacking a ketone group in the thiazine ring. Bicking and Sprague⁵² treated 1-(2-chloroethyl)benzene-2,4-disulfonylchloride derivatives (**68**) with a variety of primary amines to afford 7-sulfamoyl-3,4-dihydro-2*H*-1,2-benzothiazine 1,1-dioxides (**69**) in poor to fair overall yield. The requisite starting materials (**68**) were readily prepared by exhaustive chlorosulfonation of phenethyl halides (**67**) (Eq. 15), but the scope was limited by the concomitant introduction of a sulfamoyl substituent into the benzene ring of the 1,2-benzothiazine 1,1-dioxide (**69**).



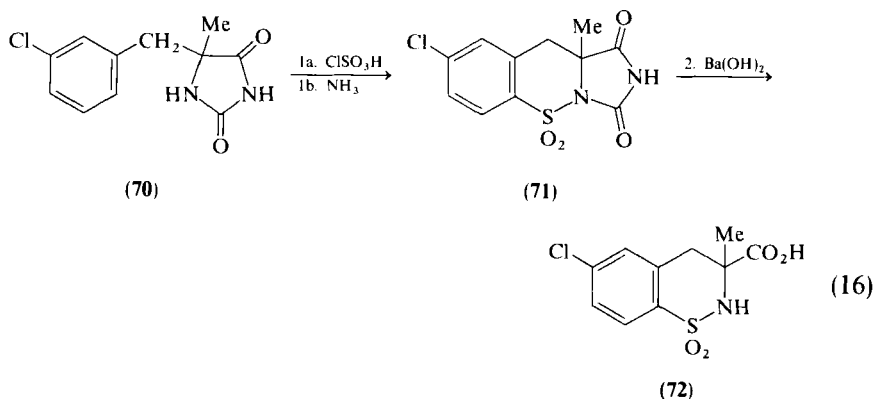
⁴⁹ P. Stoss and G. Satzinger, *Chem. Ber.* **105**, 2575 (1972).

⁵⁰ P. Stoss and G. Satzinger, German Patent 2,207,235 (1973) [*CA* **79**, 146571 (1973)].

⁵¹ P. Stoss and G. Satzinger, U.S. Patent 3,803,131 (1973) [*CA* **81**, 3979 (1974)].

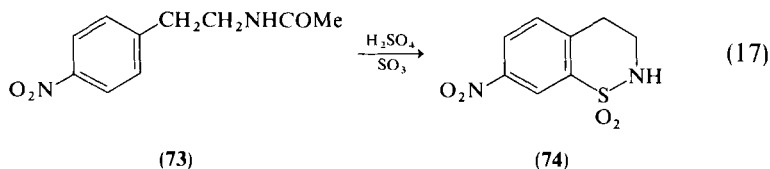
⁵² J. B. Bicking and J. M. Sprague, U.S. Patent 3,113,075 (1963) [*CA* **60**, P5514 (1964)].

In another example, Weinstock and Dunoff⁵³ selectively monochloro-sulfonated 5-(3-chlorobenzyl)-5-methylhydantoin (**70**) followed by treatment *in situ* with ammonia, which gave 8-chloro-10a-methyl-10,10a-dihydro-1*H*-imidazo[3,4-*b*][1,2]benzothiazine-1,3(2*H*)-dione 5,5-dioxide (**71**) in high yield. Basic hydrolysis of the hydantoin ring in **71** followed by loss of cyanate anion afforded 6-chloro-3-methyl-3,4-dihydro-2*H*-1,2-benzothiazine-3-carboxylic acid 1,1-dioxide (**72**) (Eq. 16).



The exclusive ortho selectivity observed in the above chlorosulfonation followed earlier observations⁵⁴ that the para directive influence of a halogen on sulfonation exceeds that of an alkyl group.

Zenno and Mizutani⁵⁵ extended this synthesis by treating *N*-(*p*-nitrophenethyl)acetamide (**73**) with fuming sulfuric acid to give 3,4-dihydro-7-nitro-2*H*-1,2-benzothiazine 1,1-dioxide (**74**) in good overall yield (Eq. 17). After reduction and diazotization, the nitro group in **74** could be replaced with a variety of other functional groups (*vide infra*).



Sianesi and co-workers⁵⁶ were able to utilize the readily available 2-(2-chloroethyl)aniline (**75**) or *o*-aminophenylacetonitrile (**48**) as starting

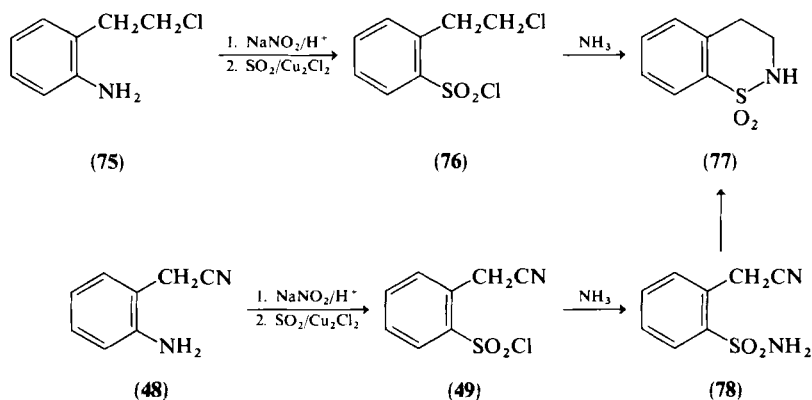
⁵³ J. Weinstock and R. Y. Dunoff, *J. Org. Chem.* **33**, 3342 (1968).

⁵⁴ C. M. Suter, "The Organic Chemistry of Sulfur," p.217. Wiley, New York, 1944.

⁵⁵ H. Zenno and T. Mizutani, Japanese Patent 44/32,404 (1969) [*CA* **72**, 79122 (1970)].

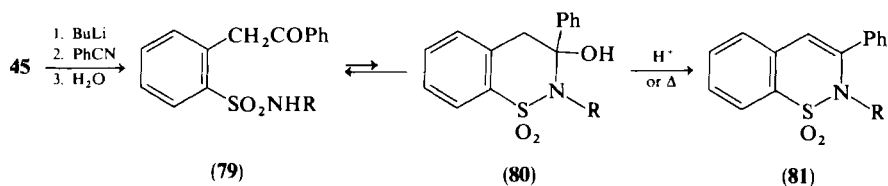
⁵⁶ E. Sianesi, P. Da Re, J. Setnikar, and E. Massarani, U.S. Patent 3,770,733 (1973) [*CA* **76**, 72535 (1972) for the equivalent German Patent 2,124,953].

materials for the preparation of 3,4-dihydro-1,2-benzothiazine 1,1-dioxide (77). Diazotization of the amino group in either of these derivatives (75 or 48) followed by treatment with $\text{SO}_2/\text{Cu}_2\text{Cl}_2$ afforded the isomerically pure sulfonyl chlorides 76 and 49 (Scheme 2). Treatment of 76 with excess ammonia gave 77 directly in high yield. Reaction of 49 with excess ammonia gave *o*-cyanomethylbenzenesulfonamide (78) which, after catalytic hydrogenation (palladium on carbon) in an acidic medium, directly cyclized to 77.



SCHEME 2

A slightly different synthetic approach was developed by Hauser and co-workers⁵⁷ while studying ring-chain tautomerization in six-membered heterocycles. The dilithiosulfonamides from 45 condensed with benzonitrile to form, after hydrolysis of the intermediate imine sulfonamides, *o*-phenacylbenzenesulfonamides (79) which were in equilibrium with the carbinol sulfonamides 80 (ring tautomer) (Scheme 3). Although infrared spectroscopy indicated that this ring-chain tautomeric mixture was almost exclusively in the open-chain form (79), dehydration of the mixture of 79 and 80 under

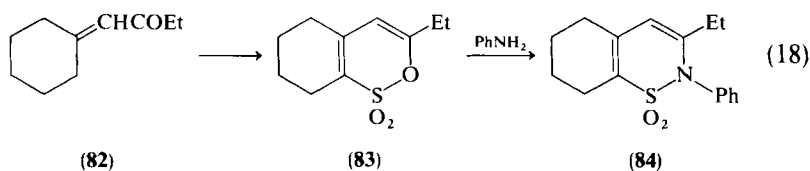


SCHEME 3

⁵⁷ H. Watanabe, C.-L. Mao, I. T. Barnish, and C. R. Hauser, *J. Org. Chem.* **34**, 920 (1969).

either acidic or thermal conditions gave 2,3-disubstituted 2*H*-1,2-benzothiazine 1,1-dioxides (**81**) in high yield.

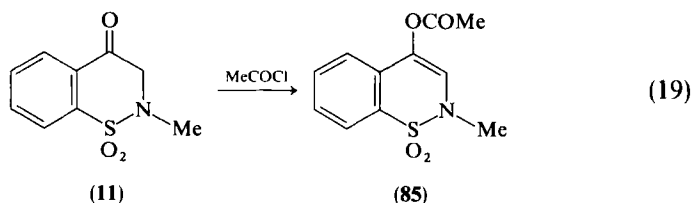
Helferich and Klebert⁵⁸ obtained the 5,6,7,8-tetrahydro-2*H*-1,2-benzothiazine 1,1-dioxide **84** by treating the bicyclic sultone derivative **83** with aniline (Eq. 18). The sultone **83** was readily prepared by reacting the α,β -unsaturated ketone **82** with sulfuric acid/acetic anhydride.



B. REACTIONS

1. 1,2-Benzothiazin-4-ones

Acylation and alkylation reactions of the enolic 4-hydroxy-1,2-benzothiazines have been studied. Zinnes *et al.*⁴ O-alkylated compound **21** with isopropyl iodide (potassium carbonate in acetone) (see Scheme 1), and formed the 4-acetoxy compound **85** from 2-methyl-2*H*-1,2-benzothiazin-4-one 1,1-dioxide (**11**) with acetyl chloride and sodium hydride (Eq. 19).⁶



Similarly, both Zinnes *et al.*^{59,60} and Rasmussen⁶¹ prepared enol carbonates **86** from the corresponding 4-hydroxy-1,2-benzothiazine-3-carbox-amides **25** and ethyl chloroformate. Excess of ethyl chloroformate in pyridine gave high yields of the O,N-bis-acylated derivative **87**.⁶²

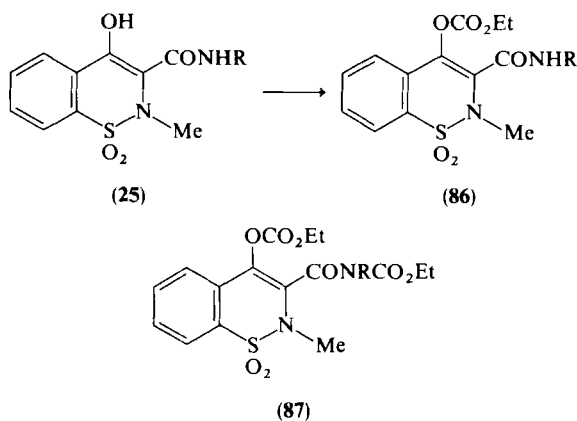
⁵⁸ B. Helferich and W. Klebert, *Justus Liebigs Ann. Chem.* **657**, 79 (1962).

⁵⁹ H. Zinnes, M. L. Schwartz, and J. Shavel, U.S. Patent 3,704,298 (1972) [*CA* **78**, 58442 (1973)].

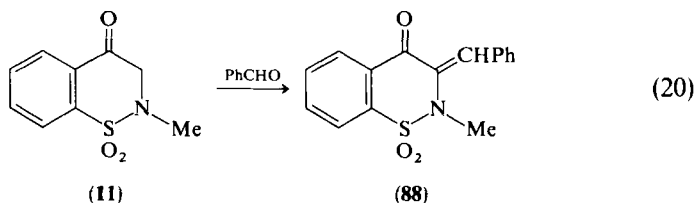
⁶⁰ H. Zinnes, N. A. Lindo, and J. Shavel, U.S. Patent 3,646,020 (1972) [*CA* **77**, 5500 (1972)].

⁶¹ C. R. Rasmussen, U.S. Patent 3,925,371 (1975) [*CA* **84**, 90162 (1976)].

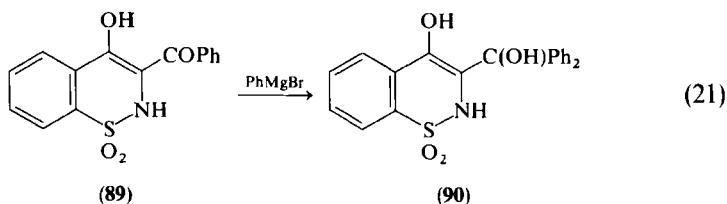
⁶² C. R. Rasmussen, U.S. Patent 3,900,470 (1975) [*CA* **83**, 193356 (1975)].



Compound **11** forms 3-alkylidene derivatives (**88**) (Eq. 20)^{4,6} with benzaldehyde and other aldehydes, including pyridine-2-carboxaldehyde.



Interesting reactions of 3-benzoyl-4-hydroxy-2*H*-1,2-benzothiazine 1,1-dioxide (**89**) have been studied by Abed.⁶³ Thus, treatment of compound **89** with phenylmagnesium bromide produced good yields of a product assigned the benzhydrol structure **90** (Eq. 21).

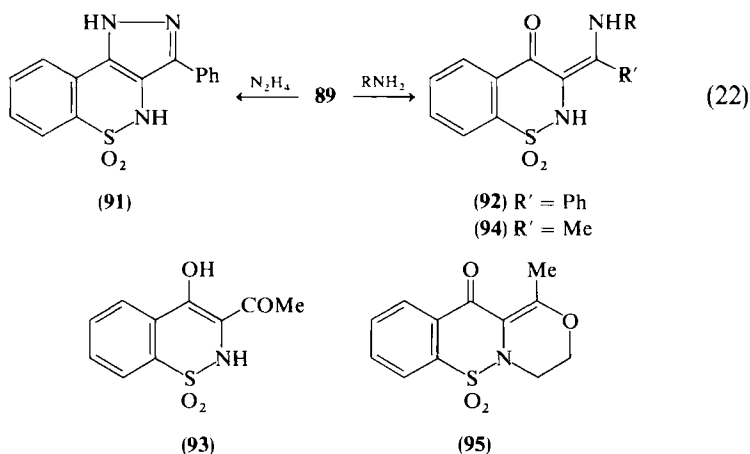


The enolic β -diketone **89** with hydrazine and amines produced excellent yields of the pyrazolo derivative **91** and the enamines **92**, respectively (Eq. 22).^{63,64} Similarly, the 3-acetyl compound **93** yielded the corresponding pyrazole when combined with hydrazine,⁶⁴ and with amines it gave the enaminketones **94**.^{8,65}

⁶³ N. M. Abed, *Indian J. Chem., Sect. B* **14**, 428 (1976).

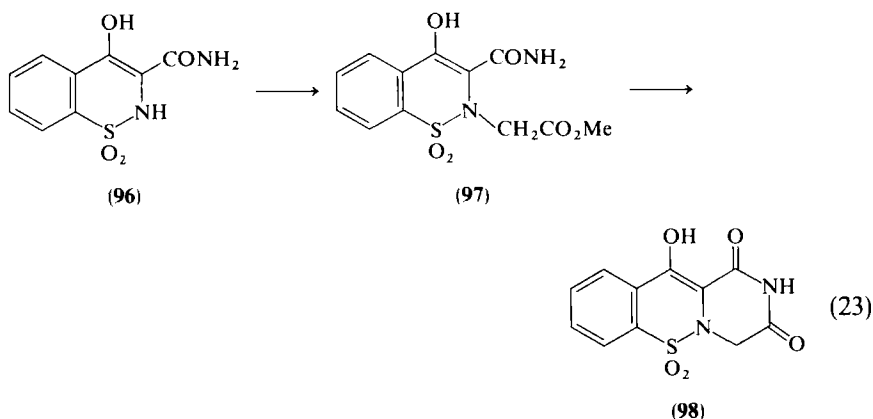
⁶⁴ J. Shavel and H. Zinnes, U.S. Patent 3,346,572 (1967) [*CA* **68**, 95839 (1968)].

⁶⁵ C. R. Rasmussen, U.S. Patent 3,476,749 (1969) [*CA* **72**, 21727 (1970)].

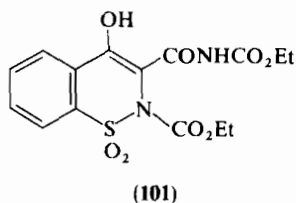
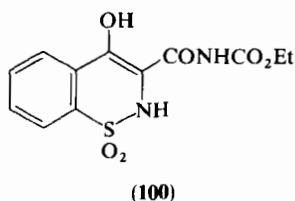
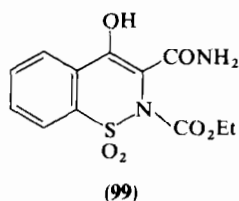


With dibromomethane compound **93** also undergoes cycloalkylation at both the oxygen and nitrogen atoms to form an oxazine (**95**).⁸ Other reactions utilizing the bifunctionality of compound **93** to produce cyclized derivatives such as **95** are discussed in greater detail in Section IV.

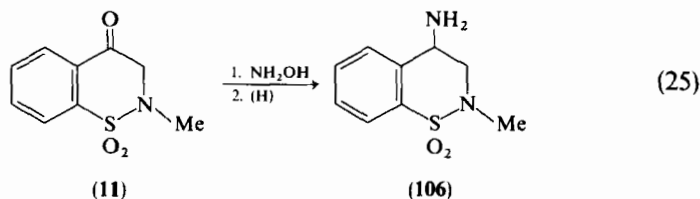
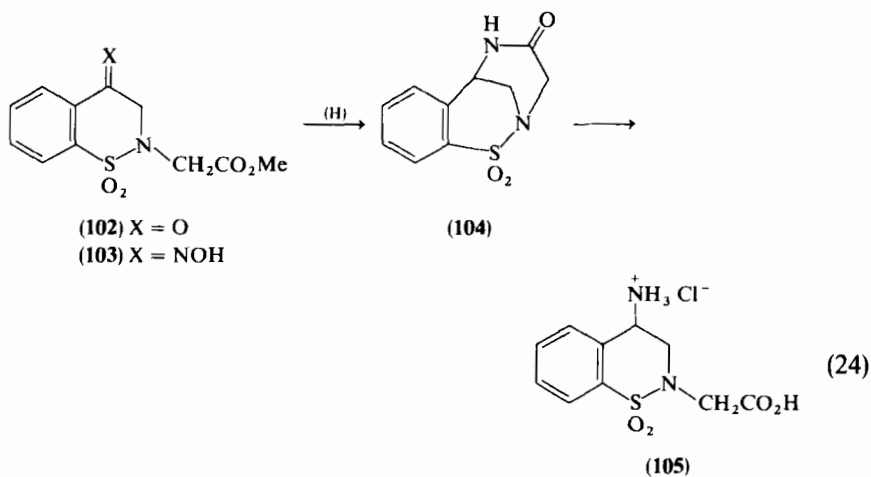
The known capacity of the sulfonamide nitrogen in 1,2-benzothiazines to undergo alkylation⁴ has been extended: **96** with methyl bromoacetate produced ester **97** which was further cyclized to the piperazine derivative **98** by sulfuric acid (Eq. 23).⁸



Surprisingly, treatment of amide **96** with ethyl chloroformate did not produce isolable yields of the expected 2-ethoxycarbonyl compound **99**. Instead, a poor yield of the 3-(*N*-ethoxycarbonylamide) **100** was obtained.⁸ The corresponding *N,N'*-diethoxycarbonyl derivative **101** was obtained when excess ethyl chloroformate was combined with **96** under alkaline conditions.⁸



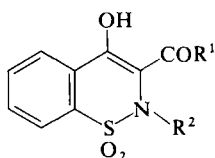
Conversion of 1,2-benzothiazin-4-one **102** to the corresponding oxime **103** followed by high-pressure catalytic hydrogenation produced the cyclized amide **104** (Eq. 24).⁶⁶ Hydrolysis of compound **104** in aqueous acid yielded the amino acid **105**. By an analogous procedure, 4-amino-3,4-dihydro-2-



⁶⁶ H. Zinnes, R. A. Comes, and J. Shavel, *J. Heterocycl. Chem.* **5**, 875 (1968).

methyl-2*H*-1,2-benzothiazine 1,1-dioxide (**106**) was made in two steps via the oxime prepared from the ketone **11** (Eq. 25).⁶

Sodium borohydride reduction of either 3-acetyl- or 3-benzoyl-4-hydroxy-2*H*-1,2-benzothiazine 1,1-dioxides (e.g., **21**, **89**, **93**) produced the corresponding 3-alkylidene compounds **108**.⁴ Evidently the intermediate alcohols are dehydrated under the conditions of the reaction. The authentic benzylidene derivative **108** ($R^1 = \text{Ph}$, $R^2 = \text{Me}$), prepared⁴ by another route (Eq. 20), was identical to the product isolated from the borohydride reduction of compound **107**.

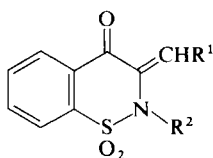


(**21**) $R^1 = R^2 = \text{Me}$

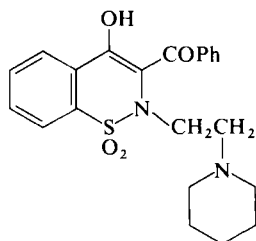
(**89**) $R^1 = \text{Ph}$, $R^2 = \text{H}$

(**93**) $R^1 = \text{Me}$, $R^2 = \text{H}$

(**107**) $R^1 = \text{Ph}$, $R^2 = \text{Me}$



(**108**)



(**109**)

In two Japanese patents, Hasegawa and co-workers^{67,68} described the preparation of 1,2-benzothiazines with 2-aminoalkyl substituents. Thus, 3-benzoyl-4-hydroxy-2*H*-1,2-benzothiazine 1,1-dioxide was alkylated by piperidinoethyl chloride to give a good yield of 1,2-benzothiazine **109**.⁶⁷

Several compounds closely related to **109** were similarly prepared with a variety of aminoalkyl substituents.⁶⁷ Alkylation of 3-thenoyl-4-hydroxy-2*H*-1,2-benzothiazine 1,1-dioxide with 2-morpholinoethyl chloride produced⁶⁸ a compound corresponding to **109**. These same workers have also prepared spirohydantoin (**110**) from 3,4-dihydro-2*H*-1,2-benzothiazin-4-one 1,1-dioxide (**10**) using potassium cyanide and ammonium carbonate (Eq. 26).⁶⁹

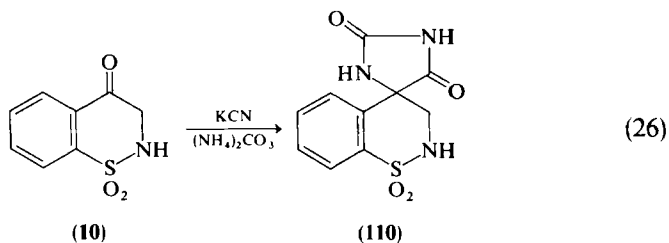
Methylation of the 3-carboxanilide **25** ($\text{Ar} = \text{Ph}$) using sodium hydride and dimethyl sulfate gave 2-*N*-dimethyl-4-hydroxy-2*H*-1,2-benzothiazine-3-carboxanilide 1,1-dioxide (**27**).⁷⁰

⁶⁷ G. Hasegawa, T. Munakata, and T. Yoshida, Japanese Patent 71/00,029 (1971) [*CA* **74**, 141828 (1971)].

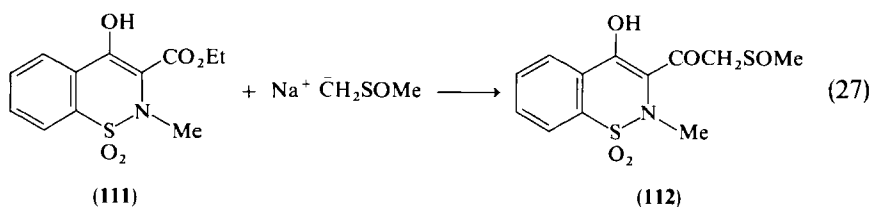
⁶⁸ G. Hasegawa, T. Munakata, T. Furuta, and T. Tsuda, Japanese Patent 71/22,027 (1971) [*CA* **75**, 76815 (1971)].

⁶⁹ G. Hasegawa, T. Munakata, and T. Furuta, Japanese Patent 70/41586 (1970) [*CA* **75**, 20423 (1971)].

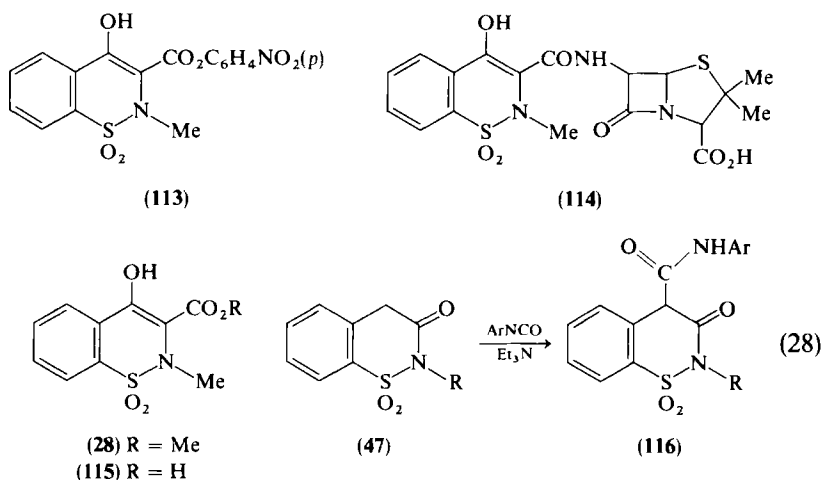
⁷⁰ H. Zinnes, N. A. Lindo, and J. Shavel, U.S. Patent 3,714,155 (1973) [*CA* **78**, 136317 (1973)].



The ethyl ester **111** and the anion of dimethyl sulfoxide produce the β -sulfinyl ketone **112** (Eq. 27).⁷¹



Acylation of 6-aminopenicillanic acid by the activated ester **113** in dichloromethane and triethylamine gave **114**.⁷²



⁷¹ M. von Strandtmann, J. Shavel, S. Klutchko, and M. Cohen, U.S. Patent 3,801,644 (1974) [CA **81**, 3595 (1974)]; U.S. Patent 3,892,739 (1975) [CA **84**, 43632 (1976)].

⁷² J. C. Sircar, H. Zinnes, and J. Shavel, U.S. Patent 3,878,198 (1975) [CA **83**, 97274 (1975)]; U.S. Patent 3,912,720 (1975) [CA **84**, 44029 (1976)]; U.S. Patent 3,966,765 (1976) [CA **86**, 5447 (1977)].

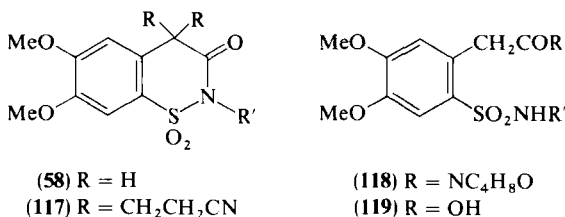
Specific conditions⁷³ hydrolyze the methyl ester **28** to the crystalline 4-hydroxy-2-methyl-2*H*-1,2-benzothiazine-3-carboxylic acid 1,1-dioxide (**115**), converted by standard methods to anti-inflammatory amides.⁷³

Heterocyclic derivatives of 3-acyl-1, 2-benzothiazin-4-one, prepared utilizing their β -diketonic nature, are discussed in Section IV.

2. 1,2-Benzothiazin-3-ones

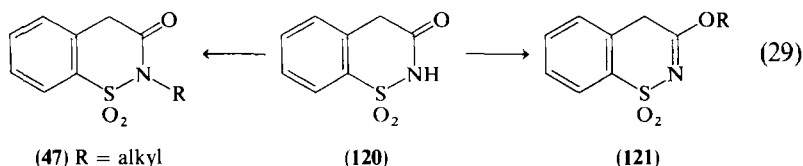
The activated 4-methylene function of 3,4-dihydro-2-alkyl-1,2-benzothiazin-3(2*H*)-one 1,1-dioxide (**47**) permits the formation of an anion. Treatment of the anion in DMSO^{14,38} or DMF⁷⁴ with isocyanates yields the corresponding 4-carboxamides (**116**) (Eq. 28).

Acrylonitrile and the anion of **58** (formed by KOH-MeOH) give the bis-cyanoethyl adduct **117**.⁷⁴ The cyclic amide bond in compound **58** was slowly cleaved by amines: morpholine at elevated temperatures affords the sulfonamide-carboxamide **118**.⁴⁶ Pyrrolidine reacts similarly.⁴⁰



Hydroxide cleaved compound **58** to the *o*-sulfamoylphenylacetic acid (**119**) in a reversal of the cyclodehydration used to prepare **58**.

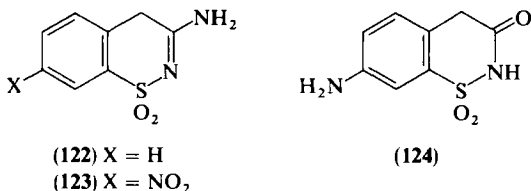
Compound **120** can be alkylated at oxygen or nitrogen, depending on the reaction conditions (Eq. 29).⁴¹ Usually, N-alkylation to **47** was observed when **120** was treated in the presence of base in DMF with alkyl halides such as propargyl chloride or allyl bromide.^{40,41} However, treating **120** in DMF with NaHCO₃ and *n*-propyl bromide produced a small amount of the *O*-alkyl compound **121** (R = *n*-propyl) as well as the *N*-alkyl derivative (**47**; R = *n*-propyl).⁴¹



⁷³ P. D. Hammen, U.S. Patent 4,100,347 (1978) [CA **88**, 105385 (1978) for equivalent German Patent 2726175].

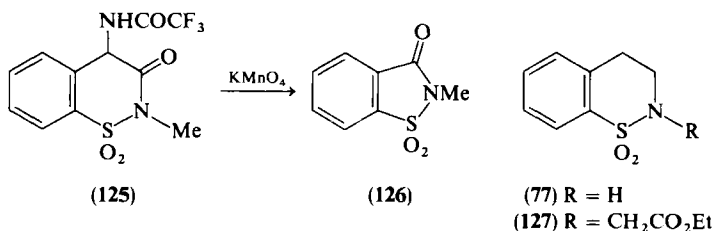
⁷⁴ P. Catsoulacos, *Chim. Ther.* **7**, 351 (1972).

Sianesi and co-workers³⁹ have nitrated the 3-amino-1,2-benzothiazine* **122** to the 7-nitro derivative **123** in good yield. Reduction and hydrolysis of **123** gave 7-amino-3,4-dihydro-3(2*H*)-one 1,1-dioxide (**124**).



The 7-amino compound **124** was carbethoxylated by ethyl chloroformate to give a 7-ethoxycarbonylamino derivative of **124**.⁴¹

Zinnes and co-workers⁴² have observed oxidative ring contraction of compound **125** to *N*-methylsaccharin (**126**) by KMnO₄ and 10% sulfuric acid at reflux.



3. Other 1,2-Benzothiazines

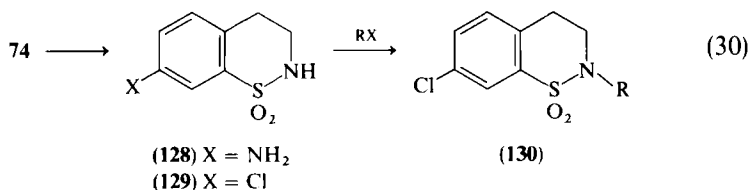
Sianesi and co-workers⁵⁶ have alkylated 3,4-dihydro-2*H*-1,2-benzothiazine 1,1-dioxide (**77**) with ethyl bromoacetate to give ethyl (3,4-dihydro-1,1-dioxo-2*H*-1,2-benzothiazin-2-yl)acetate (**127**). The ester functionality in **127** was converted into amides and hydrazides. Zenno and Mizutani⁷⁵ have also reported on the *N*-alkylation of compounds related to **77**. Alkylation of 7-chloro-3,4-dihydro-2*H*-1,2-benzothiazine 1,1-dioxide (**129**) with aralkyl halides gave the *N*-aralkyl derivatives **130** (e.g., R = CH₂Ph) in excellent overall yield (Eq. 30). The starting material **129** was prepared from the 7-nitro analog (**74**) (see Eq. 17), by a tin/hydrochloric acid reduction⁷⁶ to **128** followed by diazotization and treatment with cuprous chloride to give **129**.⁷⁷

* Compounds such as **122** are represented as 3-imino structures in the original papers.

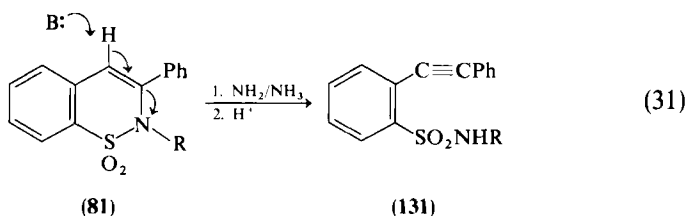
⁷⁵ H. Zenno and T. Mizutani, Japanese Patent 45/6262 (1970) [*CA* **72**, P132759 (1970)].

⁷⁶ H. Zenno and T. Mizutani, Japanese Patent 44/32405 (1969) [*CA* **72**, P79121 (1970)].

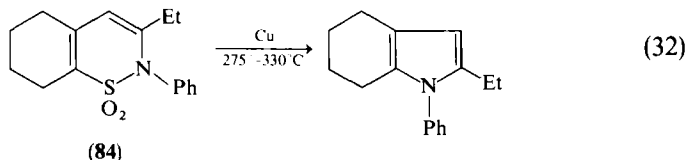
⁷⁷ H. Zenno and T. Mizutani, Japanese Patent 45/6261 (1970) [*CA* **72**, P121561 (1970)].



The only other reactions reported for these 1,2-benzothiazines led to ring cleavage. Hauser and co-workers⁵⁷ observed an intramolecular β -elimination upon treatment of **81** with either sodium amide or potassium amide in liquid ammonia, and isolated the acetylenic sulfonamide **131** in high yield (Eq. 31).



Pyrolysis of the tetrahydro-1,2-benzothiazine **84** with copper bronze eliminated sulfur dioxide and formed a fused pyrrole (Eq. 32).⁵⁸



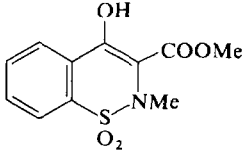
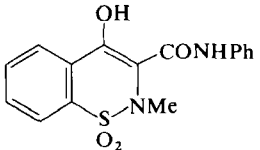
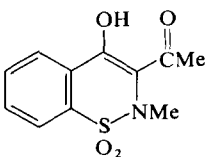
C. SPECTRAL DATA

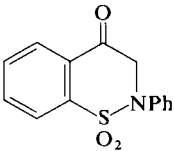
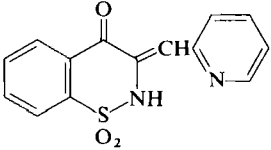
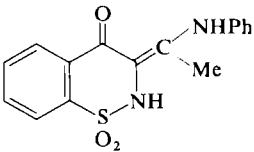
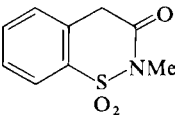
Numerous spectra recorded for 1,2-benzothiazines include the ¹³C NMR of piroxicam (**29**),⁷⁸ the electron spin resonance spectrum of the paramagnetic semidione obtained from base/oxygen oxidation of 3,4-dihydro-1,2-benzothiazin-4(2H)-one 1,1-dioxide **10**,⁷⁹ and the mass spectral fragmentations of 4-hydroxy-1,2-benzothiazines described in detail by Rasmussen⁸ and by Heyes *et al.*¹⁰ The infrared, ultraviolet, and nuclear magnetic resonance spectra of various 1,2-benzothiazines are reported.^{4,6,8-10,17,21,34,66} Representative spectral data of 1,2-benzothiazines are presented in Table I.

⁷⁸ E. B. Whipple, *Org. Magn. Reson.* **10**, 23 (1977).

⁷⁹ G. A. Russell, R. L. Blankespoor, K. D. Trahanovsky, C. S. C. Chung, P. R. Whittle, J. Mattox, C. L. Myers, R. Penny, T. Ku, Y. Kosugi, and R. S. Givens, *J. Am. Chem. Soc.* **97**, 1906 (1975).

TABLE 1
SPECTRAL PROPERTIES OF SOME 1,2-BENZOTHAZINE 1,1-DIOXIDES

Structure	Ultraviolet spectra ^a [λ_{\max} in nm (ϵ)]	Nuclear magnetic resonance spectra ^a (τ)	Infrared spectra ^a (μ)	Reference
		[CDCl ₃] - 2.04 (enol OH), 6.05 (OMe), 1.8-2.4 (C ₆ H ₄), 7.06 (NMe)		9
		[CDCl ₃] - 3.44 (enol OH), 1.67 (NH), 1.82-3.0 (C ₆ H ₄), 7.13 (NMe)	[KBr] 2.95, 6.08, 6.21, 6.46	9
	[95% EtOH] 245-248 (6100) 320 (11,000) [NaOH/EtOH] 242 (11,400) 354 (11,200)		[Nujol] 6.18, 6.28, 6.47	4

		$[\text{CCl}_4]$ 2.2 (C_6H_4), 3.1 (Ph), 4.93 (CH_2)	$[\text{?}]$ 5.84, 6.30, 7.46, 8.06	10
	$[\text{95\% EtOH}]$ 282 (12,800) 462 (12,400)		$[\text{Nujol}]$ 3.21, 5.99, 6.12, 6.27, 6.37	6
	$[\text{MeOH}]$ 256 (13,600) 382 (17,100)		$[\text{CHCl}_3]$ 2.95, 6.22	8
		$[\text{CDCl}_3]$ 2.1 (C_6H_4), 5.78 (CH_2), 6.83 (NMe)	$[\text{KBr}]$ 5.81, 7.45, 8.48	38

^a The compounds in brackets are "solvents."

D. UTILITY

Biological activities have been found for 1,2-benzothiazines. The ethyl ester **111** causes ventricular arrhythmia in dogs⁸⁰ and rats^{81,82} and was suggested as a biological tool for testing for antiarrhythmic agents. Diuretic activity was detected in a family of 5-chloro-6-sulfamoyl-3-acyl-1,2-benzothiazines.¹³ 1,2-Benzothiazines with basic side chains, for example compound **109**, are claimed⁶⁸ to be diuretic, anti-inflammatory, and antibacterial agents. Spirohydantoin such as compound **110** are diuretic, hypoglycemic, analgesic, and fungicidal agents.⁷⁰ Antithrombotic⁸³ and lipid-regulating⁸⁴ properties are observed for 4-hydroxy-1,2-benzothiazine-3-carboxamides. Antibacterial activity was found for several penicillin derivatives containing a 1,2-benzothiazinyl fragment.⁷²

By far the greatest number of reports have referred to the anti-inflammatory activity found for a variety of 1,2-benzothiazines.¹⁵ An initial report by Lombardino *et al.*⁹ indicated that potent anti-inflammatory activity was present in a series of 4-hydroxy-2*H*-1,2-benzothiazine-3-carboxanilide 1,1-dioxides. Antiedema activity in a rat model indicated that carboxanilide **132** (CP-14, 304) was twice as potent as the standard anti-inflammatory agent phenylbutazone. This observation on compound **132** was later confirmed and extended by others.^{17,85} Studies of the metabolism of compound **132** in animals indicated that a major metabolite resulted from hydroxylation of the carboxanilide moiety.⁸⁶ The plasma half-life of compound **132** was found to be 21 hours in man.⁸⁶

As extensions of the findings with compound **132**, Lombardino and Wiseman¹⁹ prepared *N*-heterocyclic carboxamides of 4-hydroxy-2*H*-1,2-benzothiazine 1,1-dioxide including the potent anti-inflammatory sudoxicam (**20**).^{19,21} Sudoxicam is significantly more acidic (pK_a' 5.3) and a more potent⁸⁷ anti-inflammatory agent than the carboxanilide **132**. An internally hydrogen-bonded enolate was suggested as a possible explanation of enhanced acidity.²¹ The plasma half-life of sudoxicam is extended²¹ and

⁸⁰ T. P. Pruss, *Toxicol. Appl. Pharmacol.* **14**, 1 (1969) [*CA* **70**, 86130 (1969)].

⁸¹ A. Ferrari, G. Razzaboni, and W. Vergoni, *Riv. Farmacol. Ter.* **1**, 161 (1970) [*CA* **75**, 150161 (1971)].

⁸² A. Ferrari, G. Razzaboni, and W. Vergoni, *Riv. Farmacol. Ter.* **1**, 303 (1970) [*CA* **75**, 117040 (1971)].

⁸³ J. G. Lombardino and E. H. Wiseman, U.S. Patent 3,862,319 (1975) [*CA* **83**, 72175 (1975)].

⁸⁴ J. G. Lombardino and G. F. Holland, U.S. Patent 3,674,876 (1972) [*CA* **77**, 109576 (1972)].

⁸⁵ G. DiPasquale, C. L. Rassaert, R. S. Richter, and L. V. Tripp, *Arch. Int. Pharmacodyn. Ther.* **203**, 92 (1973).

⁸⁶ J. Chiaini, E. H. Wiseman, and J. G. Lombardino, *J. Med. Chem.* **14**, 1175 (1971).

⁸⁷ E. H. Wiseman and J. Chiaini, *Biochem. Pharmacol.* **21**, 2323 (1972).

the products of metabolism, resulting from thiazole ring scission, have been identified.⁸⁸ Other activities of sudoxicam include inhibition of platelet aggregation,^{89,90} antithrombotic activity,⁹¹ inhibition of rabbit monoarticular arthritis,⁹² inhibition of leukocyte migration,^{93,94} and delay of castor oil diarrhea in rats.⁹⁵ Sudoxicam exhibited more potent anti-inflammatory activity in animals than 14 other acidic anti-inflammatory agents.⁹⁶ Other *N*-thiazolylcarboxamide derivatives of 1,2-benzothiazines are also claimed to be potent anti-inflammatory agents.^{97,98}

Another *N*-heterocyclic 1,2-benzothiazine-3-carboxamide related to sudoxicam is the *N*-(5-methyl-3-isoxazolyl) derivative isoxicam (**43**),⁹⁹⁻¹⁰¹ with moderate anti-inflammatory activity^{99,101} and low ulcerogenic potential.^{99,102} Compound **43** is prepared by several routes including combination of 3-amino-5-methylisoxazole with the ester **111** in xylene,^{103,104} preparation of an enamine and acylation with phosgene (Eq. 6),^{17,22,23} and rearrangement of a benzisothiazoline acetamide (**40**) (Eq. 9).³⁶ The metabolism of isoxicam involves cleavage of the isoxazole ring.¹⁰⁵ Only modest effects of isoxicam on prostaglandin biosynthesis have been

⁸⁸ D. C. Hobbs and T. M. Twomey, *Drug Metab. Dispos.* **5**, 75 (1977).

⁸⁹ J. W. Constantine and I. Purcell, *J. Pharmacol. Exp. Ther.* **187**, 653 (1973).

⁹⁰ R. Kadatz, in "Platelet Aggregation in the Pathogenesis of Cerebrovascular Disorders" (A. Agnoli and C. Fazio eds.), p.216. Springer-Verlag, Berlin and New York, 1977 [*CA* **88**, 58319 (1978)].

⁹¹ J. G. Lombardino and E. H. Wiseman, French Demande 2,052,924 (1971) [*CA* **76**, 103755 (1972)].

⁹² A. Blackham and H. Radziwonik, *Agents Actions* **7**, 473 (1977).

⁹³ A. Blackham and R. T. Owen, *J. Pharm. Pharmacol.* **27**, 201 (1975).

⁹⁴ I. Rivkin, G. V. Foschi, and C. H. Rosen, *Proc. Soc. Exp. Biol. Med.* **153**, 236 (1976).

⁹⁵ F. Awouters, C. J. E. Niemegeers, F. M. Lenaerts, and P. A. J. Jansen, *J. Pharm. Pharmacol.* **30**, 41 (1978).

⁹⁶ J. G. Lombardino, I. G. Otterness, and E. H. Wiseman, *Arzneim.-Forsch.* **25**, 1629 (1975).

⁹⁷ K. Thomae GmbH., Netherlands Patent Application 75/12,271 (1976) [*CA* **86**, 72677 (1977)]; also Belgian Patent 835,392 (1976) and German Patent 2452996 (1976).

⁹⁸ K. Thomae GmbH., German Patent 2756113 (1979); European Patent 2-482 (1979).

⁹⁹ G. DiPasquale, C. Rassaert, R. Richter, P. Welaj, J. Gingold, and R. Singer, *Agents Actions* **5**, 256 (1975).

¹⁰⁰ G. DiPasquale, C. Rasser, P. Welaj, and L. Tripp, *Agents Actions* **6**, 748 (1976).

¹⁰¹ G. DiPasquale, C. Rassaert, P. Welaj, J. Gingold, and E. Schwartz, *Res. Commun. Chem. Pathol. Pharmacol.* **19**, 529 (1978).

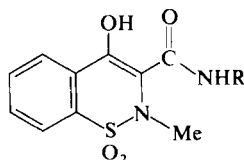
¹⁰² K. D. Rainsford, *Agents Actions* **7**, 573 (1977).

¹⁰³ H. Zinnes, M. L. Schwartz, and J. Shavel, U.S. Patent 3,787,324 (1974); U.S. Patent 3,816,628 (1974) [*CA* **77**, 164722 (1972) for equivalent German Patent 2,208,351].

¹⁰⁴ J. D. Genzler and F. C. Fontser, U.S. Patent 4,024,136 (1977) [*CA* **87**, 68398 (1977)]; U.S. Patent 3,960,856 (1976) [*CA* **85**, 46728 (1976)].

¹⁰⁵ J. P. Viau, J. E. Epps, and F. J. DiCarlo, *Fed. Proc., Fed. Am. Soc. Exp. Biol.* **34**, 734 (1975).

observed.¹⁰⁶ An isomeric analog of isoxicam [4-hydroxy-2-methyl-*N*-(3-methyl-5-isoxazolyl)-2*H*-1,2-benzothiazine-3-carboxamide 1,1-dioxide] also exhibited anti-inflammatory activity.¹⁰⁷

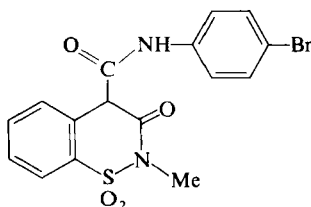


(20) R = 2-thiazolyl

(29) R = 2-pyridyl

(43) R = 5-methylisoxazol-3-yl

(132) R = Ph



(133)

Much literature exists on the potent anti-inflammatory agent piroxicam (29). Lombardino, Wiseman, and co-workers have described the synthesis and potent antiedema activity of piroxicam in animals.^{19–21} The biotransformation products of piroxicam in animals¹⁰⁸ and man¹⁰⁹ have been reported. Piroxicam is an inhibitor of platelet aggregation¹¹⁰ and a potent inhibitor of prostaglandin biosynthesis in cultures of either MC5-5 cells or synovial cells.¹¹¹ In man, piroxicam has a long half-life (45 h)¹¹² and is effective in the treatment of rheumatoid arthritis,^{113,114} osteoarthritis,¹¹⁵ and other painful musculoskeletal conditions^{116–119} when administered as

¹⁰⁶ G. DiPasquale and D. Mellace, *Agents Actions* **7**, 481 (1977).

¹⁰⁷ H. Zinnes, M. L. Schwartz, N. A. Lindo, and J. Shavel, U.S. Patent 3,868,367 (1975) [CA **82**, 170994 (1975)].

¹⁰⁸ D. C. Hobbs and T. M. Twomey, *Pharmacologist* **18**, 152 (1976).

¹⁰⁹ T. M. Twomey and D. C. Hobbs, *Fed. Proc. Fed. Am. Soc. Exp. Biol.*, **37**, 271 (1978).

¹¹⁰ B. J. Gaynor and J. W. Constantine, *Experientia* **35**, 797 (1979).

¹¹¹ T. J. Carty, J. Eskra, J. G. Lombardino, and W. W. Hoffman, *Prostaglandins* **19**, 51 (1980).

¹¹² D. C. Hobbs and T. M. Twomey, *J. Clin. Pharmacol.* **19**, 270 (1979).

¹¹³ M. Weintraub, R. F. Jacox, C. D. Angevine, and E. C. Atwater, *J. Rheumatol.* **4**, 393 (1977).

¹¹⁴ W. M. O'Brien and E. H. Wiseman, eds., *Piroxicam*, Royal Society of Medicine International Congress and Symposium Series, No. 1. Academic Press, New York, 1978.

¹¹⁵ H. Telhag, *Eur. J. Rheumatol. Inflammation* **1**, 352 (1978).

¹¹⁶ P. Widmark, *Eur. J. Rheumatol. Inflammation* **1**, 346 (1978).

¹¹⁷ A. K. Jain, F. G. McMahon, J. R. Ryan, H. Raphan, and W. Richard, *Eur. J. Rheumatol. Inflammation* **1**, 356 (1978).

¹¹⁸ I. Radi, L. Matoso, A. Posmantir, and P. Papalexou, *Eur. J. Rheumatol. Inflammation* **1**, 349 (1978).

¹¹⁹ E. H. Wiseman, *Eur. J. Rheumatol. Inflammation* **1**, 338 (1978).

a single daily dose of 20 mg. The history of the discovery of piroxicam has been reviewed¹²⁰; it is presently marketed in Europe.

The 4-carboxamides of 1,2-benzothiazin-3(2*H*)-one 1,1-dioxide also exhibit anti-inflammatory activity.^{14,38} Several analogs, including the 4-bromocarboxanilide compound **133**, were equivalent to indomethacin in anti-inflammatory potency in animals.³⁸

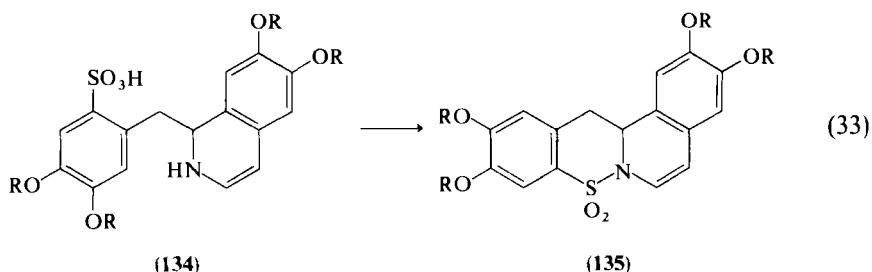
Both hypnotic and anticonvulsant activity were observed when fairly high doses of 2-alkyl-3,4-dihydro-1,2-benzothiazin-3(2*H*)-one 1,1-dioxide (**47**) were administered to mice.^{40,41}

Stoss has reported⁵¹ antisecretory activity for sulfoximides (**64**) derived from 1,2-benzothiazin-3-ones.

Sianesi and co-workers⁵⁶ claimed hypnotic and anticonvulsant activity for amides and hydrazides prepared from the 1,2-benzothiazine ester **127**.

III. Naphtho- and Dibenzo-1,2-thiazines

Compounds in this section are discussed in order of the point of fusion of an aromatic ring to the 1,2-benzothiazine nucleus. Klivenyi and co-workers,¹²¹ in attempting to prepare derivatives of papaverine-6'-sulfonic acid (**134**), reacted **134** with chlorosulfonic acid and isolated in good yield 2, 3, 10, 11-tetraalkoxy-7, 8-dihydroisoquinolino [2, 1-*b*] [1, 2]benzothiazine 8,8-dioxide (**135**), a naphtho-1,2-benzothiazine analog (Eq. 33).



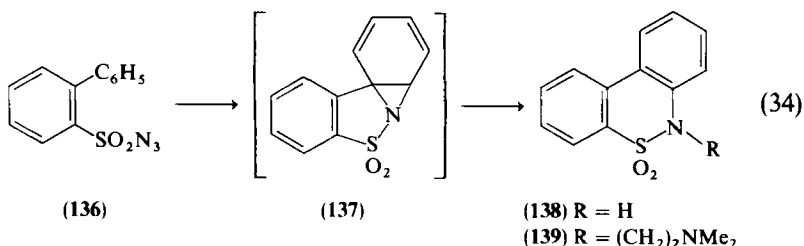
Abramovitch and co-workers,¹²² investigating the chemistry of aryl-nitrenes and sulfonylnitrenes, thermolyzed biarylsulfonyl azides (**136**) which at 120°C produced 6*H*-dibenzo[*c,e*][1,2]thiazine 5,5-dioxide (**138**) (80%) via the proposed intermediate **137** (Eq. 34). N-Alkylation of **138** with

¹²⁰ E. H. Wiseman and J. G. Lombardino, in "Chronicles of Drug Discovery" (J. S. Bindra and D. Lednicer, eds.), Wiley, New York, 1981.

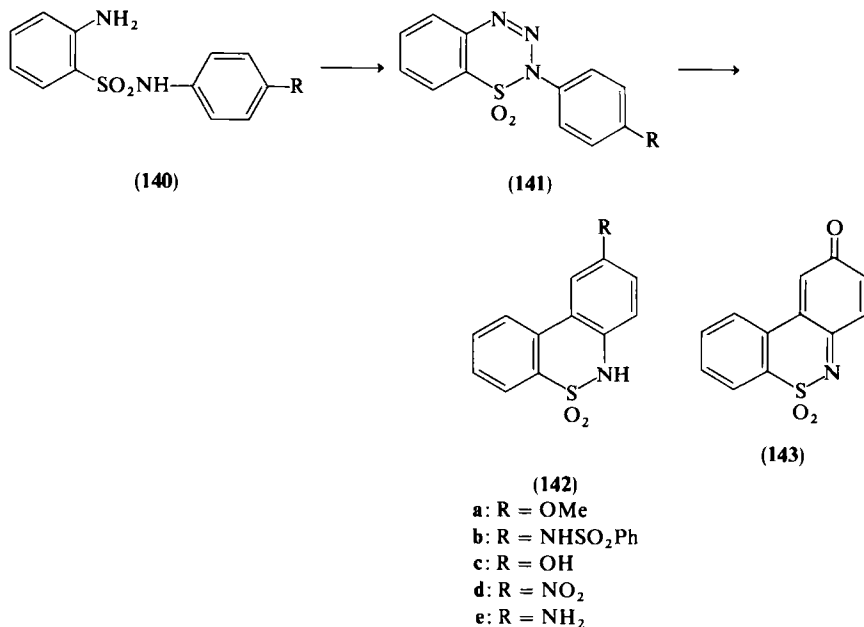
¹²¹ F. Klivenyi, E. Vinkler, and G. Dombi, *Pharmazie* **33**, 379 (1978).

¹²² R. A. Abramovitch, T. Chellathurai, J. T. McMaster, T. Takaya, C. I. Azogu, and D. P. Vanderpool, *J. Org. Chem.* **42**, 2914 (1977).

β -dimethylaminoethyl chloride gave *N*-(2-dimethylaminoethyl)-6*H*-dibenzo-*[c,e]*[1,2]thiazine 5,5-dioxide (**139**). Ring-substituted derivatives of **138** have also been prepared.



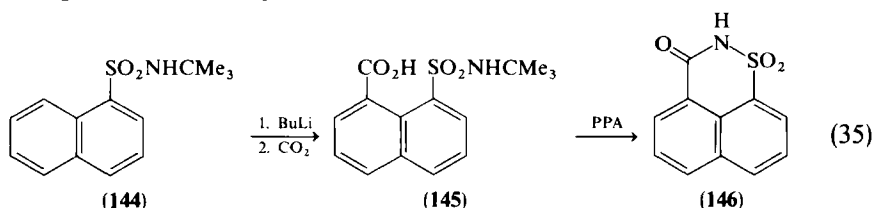
Burmistrov *et al.*¹²³ prepared 9-methoxy- (or 9-phenylsulfamido-) dibenzo-*[c,e]*[1,2]thiazine 5,5-dioxide (**142**). Diazotization of **140** gave 2-(4-substituted-phenyl)benzo-1,2,3,4-thiatriazine 1,1-dioxide (**141**) which was treated with sodium hydroxide and copper powder to afford **142**. 9-Hydroxydibenzo-*[c,e]*[1,2]thiazine 5,5-dioxide (**142c**) was prepared by demethylation of **142a**. The same workers showed that nitration of **138** afforded the 9-nitro derivative **142d**. Reduction of **142d** to the amino derivative (**142e**) followed by treatment with benzenesulfonyl chloride gave **142b**.



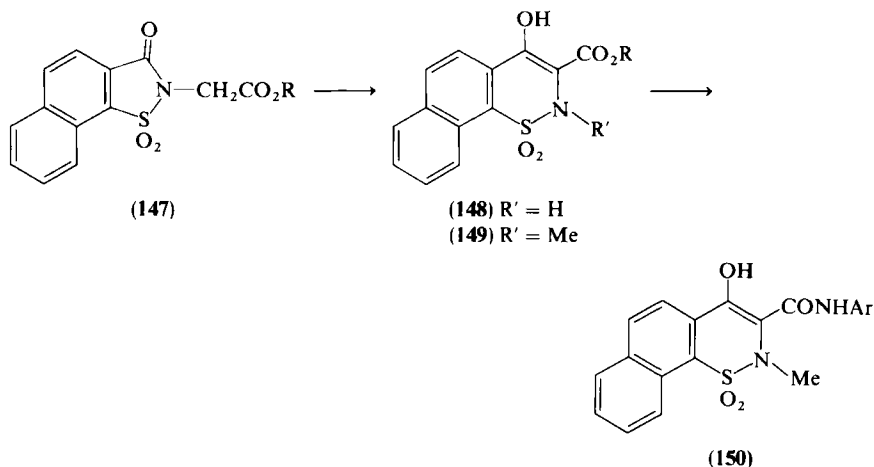
¹²³ K. S. Burmistrov, S. I. Burmistrov, and M. S. Malinovskii, *Khim. Geterotsikl. Soedin.*, 1503 (1977) [*CA* **88**, 89599 (1978)].

Oxidation of **142c** with lead tetraacetate gave 9*H*-9-oxodibenzo[*c,e*][1,2]-thiazine 5,5-dioxide (**143**). The redox potentials of some 9-substituted dibenzo[*c,e*][1,2]thiazine 5,5-dioxides (**142**) have been determined.¹²³

Kaufmann and Zobel¹²⁴ first prepared 2,3-dihydro-3-oxonaphtho[1,8-*d,e*][1,2]thiazine 1,1-dioxide (**146**). More recently, this was prepared by Lombardino¹²⁵ by an abbreviated process involving lithiation of **144** and treatment with carbon dioxide (Eq. 35). Cyclization of **145** with polyphosphoric acid simultaneously removed the *tert*-butyl group to produce compound **146** directly.



Both Trummlitz *et al.*¹²⁶ and Steiner¹²⁷ appear independently to have prepared naphtho [2,1-*e*]-1,2-thiazine analogs of the potent "oxicam" anti-inflammatory agents by the reaction sequence of Scheme 4. 3-Oxonaphth-[2,1-*d*]isothiazoline-2-acetic ester 1,1-dioxides (**147**) (R = Me or Et) were



SCHEME 4

¹²⁴ H. Kaufmann and H. Zobel, *Chem. Ber. B* **55**, 1499 (1922).

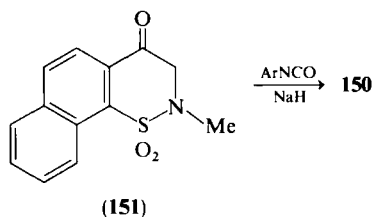
¹²⁵ J. G. Lombardino, *J. Org. Chem.* **36**, 1843 (1971).

¹²⁶ G. Trummlitz, E. Seeger, W. Engel, H. Teufel, G. Englehardt, and W. Haarmann, U.S. Patent 3,992,535 (1976) [*CA* **86**, 72677 (1977) and **87**, 53339 (1977) for the equivalent German patents 2,452,996 and 2,539,112, respectively].

¹²⁷ G. Steiner, *Justus Liebigs Ann. Chem.*, 635 (1978).

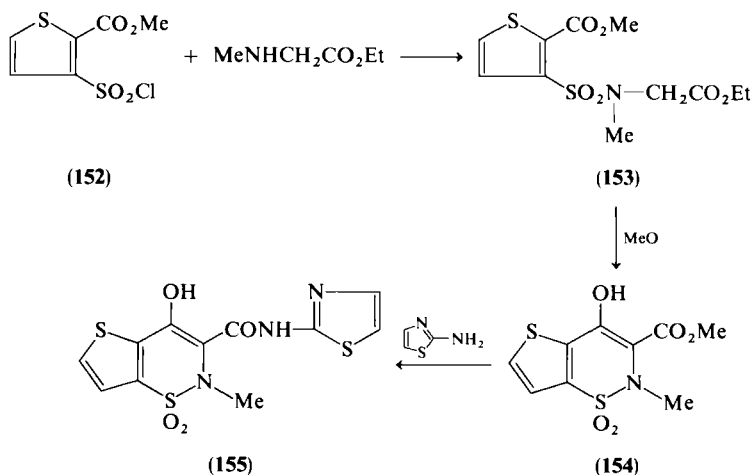
converted in a standard manner to 4-hydroxy-2*H*-naphtho[2,1-*e*]-1,2-thiazine-3-carboxylate 1,1-dioxides (**148**) by heating with sodium methoxide in *tert*-butyl alcohol. Alkylation of (**148**) with methyl iodide gave **149**, which when heated with aromatic or heteroaromatic amines in xylene yielded the desired amides **150**.

Trummelitz and co-workers¹²⁶ also prepared derivatives of **150** by treatment of 2-methyl-2*H*-naphtho [2,1-*c*] [1,2]thiazin-4-(3*H*)-one 1,1-dioxide (**151**) with sodium hydride and an aryl isocyanate. The starting material (**151**) for this sequence was synthesized analogously to the related benzo-thiazine **11**.



IV. Heterocyclic Ring-Fused 1,2-Thiazines

The outstanding anti-inflammatory activity exhibited by sudoxicam (**20**), and piroxicam (**29**) (see Section II,D) has prompted exploration of structure-activity relationships (SAR) of "oxicam" anti-inflammatory agents. This

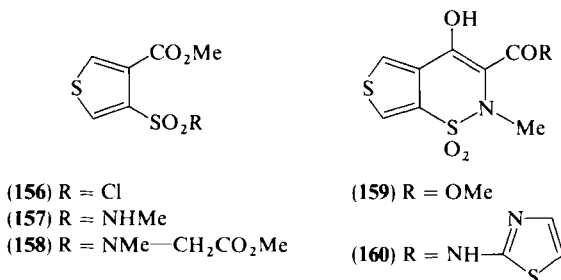


SCHEME 5

effort has included the replacement of the benzo portion of the 1,2-benzothiazine molecule with heteroaromatic rings.

The preparation of two of the three possible isomeric thieno-1,2-thiazin-4-ones (Schemes 5 and 6)¹²⁸ involved reactions reported¹² for the corresponding benzothiazines (see Scheme 1). Thus, methyl 3-chlorosulfonylthiophene-2-carboxylate (**152**) with sarcosine ethyl ester gave thiophene sulfonamide (**153**) which, with methanolic sodium methoxide, yielded 3-methoxycarbonyl-4-hydroxy-2-methyl-2*H*-thieno[2,3-*e*]-1,2-thiazine 1,1-dioxide (**154**). Heating **154** with 2-aminothiazole gave **155**, a thieno-1,2-thiazine analog of sudoxicam (**20**) (Scheme 5).

Analogously, methyl 4-chlorosulfonylthiophene-3-carboxylate (**156**) was converted to 4-hydroxy-3-methoxycarbonyl-2-methyl-2*H*-thieno[3,4-*e*]-1,2-thiazine 1,1-dioxide (**159**), which with 2-aminothiazole gave **160**.

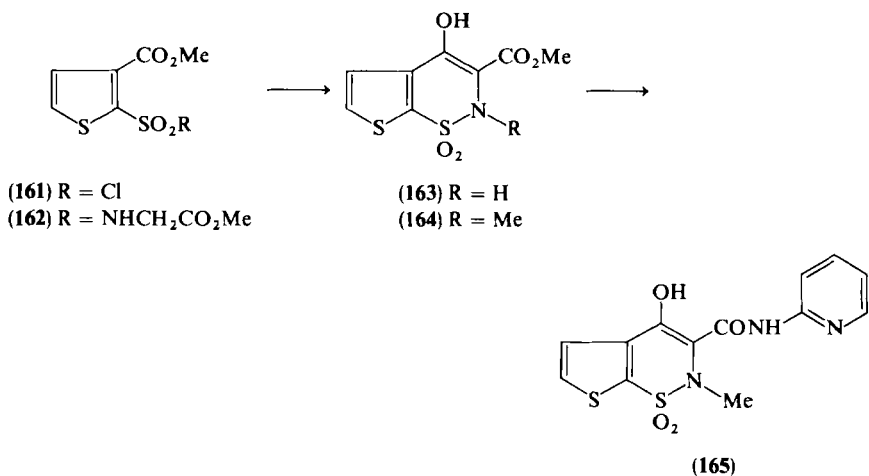


Pfister and co-workers¹²⁹ recently prepared derivatives of the third possible thieno-1,2-thiazin-4-one. Methyl 2-chlorosulfonylthiophene-3-carboxylate (**161**) with glycine methyl ester gave intermediate **162**, which afforded 4-hydroxy-3-methoxycarbonyl-2*H*-thieno[3,2-*e*]-1,2-thiazine 1,1-dioxide (**163**) upon heating with base. Alkylation of **163** with methyl iodide/sodium hydride gave **164** which afforded a thieno-1,2-thiazine analog (**165**) of piroxicam (**29**) when heated with 2-aminopyridine (Scheme 6).

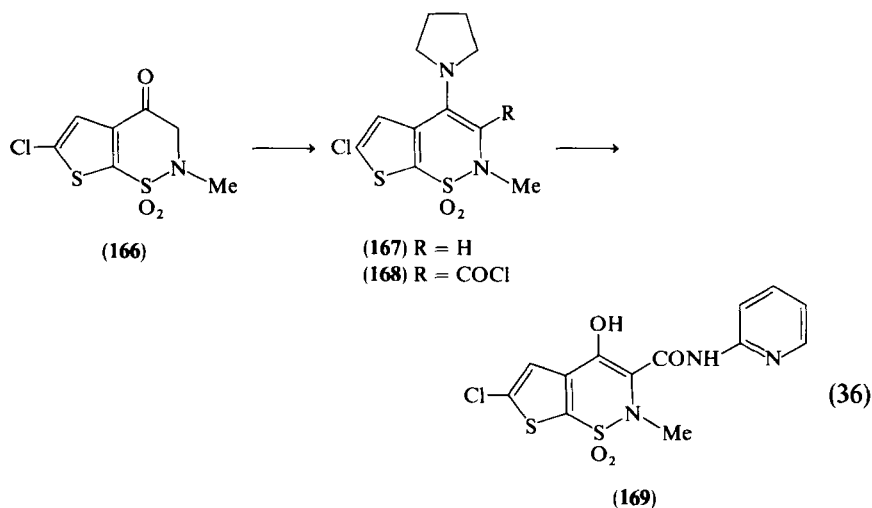
A number of halogenated derivatives of **155**, **160**, and **165** have been prepared.¹²⁹ For example, the thieno-1,2-thiazine analog **166** has been converted to enamine derivative **167** which has been acylated (phosgene/triethylamine) to afford acid chloride **168**. Treatment of **168** with 2-aminopyridine gave **169** (Eq. 36). This process is completely analogous to the 1,2-benzothiazine synthesis depicted in Eq. (6).

¹²⁸ O. Hromatka, D. Binder, R. Pfister, and P. Zeller, U.S. Patent 4,076,709 (1978) [*CA* **85**, 63077 (1976) for the equivalent Belgian Patent 832,707]. Related subject matter is disclosed in British Patents 1,519,811 and 1,519,812 (1978).

¹²⁹ R. Pfister, P. Zeller, D. Binder, and O. Hromatka, British Patent 2,003,877 (1979) [*CA* **91**, 5233 (1979) for equivalent German Patent 2,838,851].

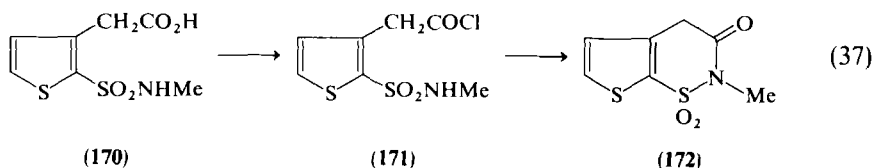


SCHEME 6

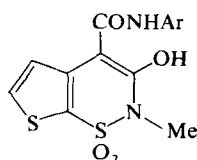


Pfister and co-workers¹³⁰ have also prepared the three isomeric thieno-1,2-thiazine-3-one ring systems. The acid chloride 171 of 3-(2-*N*-methylsulfamoyl)thiopheneacetic acid (170) with sodium bicarbonate gave 3,4-dihydro-2-methyl-3-oxo-2*H*-thieno[3,2-*e*]-1,2-thiazine 1,1-dioxide (172) (Eq. 37).

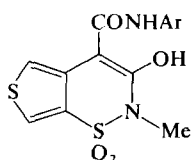
¹³⁰ R. Pfister, P. Zeller, D. Binder, and O. Hromatka, British Patent 2,002,771 (1979) [*CA* **90**, 203568 (1979) for equivalent German Patent 2,835,760]; U.S. Patent 4,090,020 (1978) [*CA* **87**, 201563 (1977) for equivalent Belgian Patent 851,686].



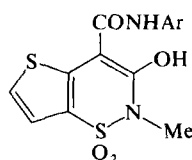
Treatment of **172** with aromatic or heteroaromatic isocyanates yielded the expected 4-carbamoyl derivatives **173** claimed to have anti-inflammatory activity.¹³⁰ 4-Carbamoyl-3,4-dihydro-3-hydroxy-2-methyl-2H-thieno[3,4-*e*]- and [2,3-*e*]-1,2-thiazine 1,1-dioxides (**174** and **175**) were prepared analogously (cf. Section II,A,2).¹³⁰



(173)

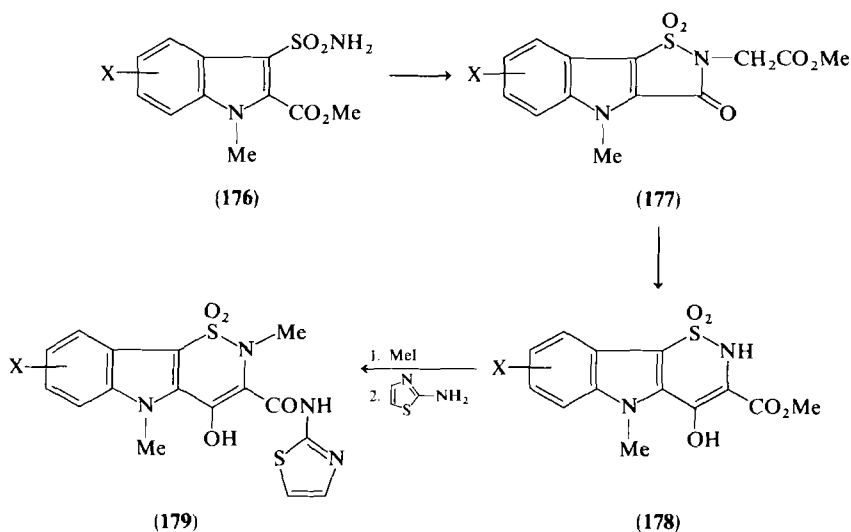


(174)



(175)

Indole derivatives¹³¹ of sudoxicam (**20**) have been prepared (Scheme 7): methyl 1-methyl-3-sulfamoylindole-2-carboxylate (**176**) gave with sodium



SCHEME 7

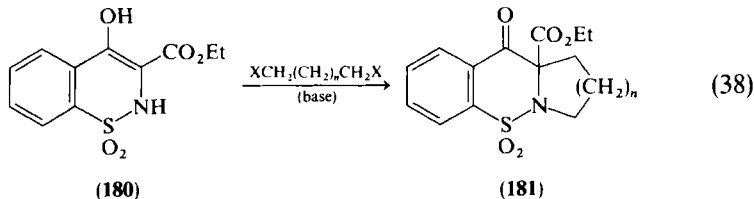
¹³¹ G. Trummlitz, W. Engel, E. Seeger, W. Haarmann, and G. Engelhardt, U.S. Patent 4,137,313 (1979) [CA **89**, 163592 (1978) for equivalent German Patent 2,704,485].

methoxide in methanol the intermediate 4-methyl-2*H*-isothiazolo[4,5-*b*]-indole-3-(4*H*)-one 1,1-dioxide sodium salt which, when treated with methyl chloroacetate, gave methyl 3,4-dihydro-4-methyl-3-oxo-2*H*-isothiazolo-[4,5-*b*]indole-2-acetate 1,1-dioxide (**177**) (>90%). Ring expansion of **177** (sodium methoxide/toluene) gave methyl 2,5-dihydro-4-hydroxy-5-methyl-1,2-thiazino[5,6-*b*]indole-3-carboxylate 1,1-dioxide (**178**). Alkylation of **178** (sodium hydroxide/methyl iodide) followed by aminolysis afforded the sudoxicam analog **179** in good overall yield (Scheme 7). Other synthetic routes (see Section II,A,1) for similarly substituted 1,2-benzothiazines have also been used for these thiazino[5,6-*b*]indoles.¹³¹

V. Ring-Fused 1,2-Benzothiazine Derivatives

The two preceding sections have discussed replacement of the benzene ring of a 1,2-benzothiazine with other aromatic or heteroaromatic systems. This section details reactions of 1,2-benzothiazines leading to more complex tri- and tetracyclic 1,2-benzothiazine ring systems.

Rasmussen^{8,132} obtained tricyclic, 1,2-benzothiazines (**181**) from ethyl 4-hydroxy-2*H*-1,2-benzothiazine-3-carboxylate 1,1-dioxide (**180**) and α,ω -dihalides (e.g., 1, 3-dibromopropane) (Eq. 38).

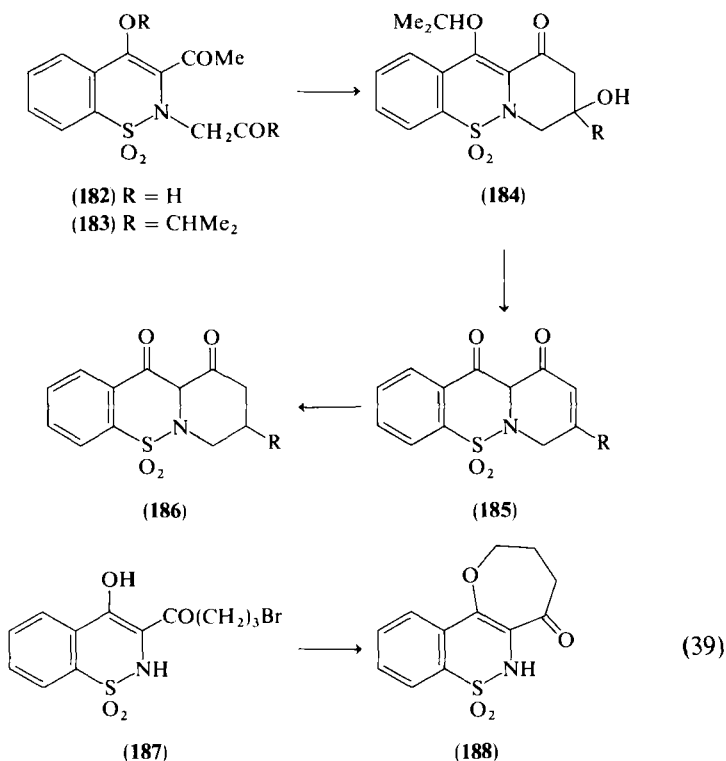


Zinnes and co-workers^{133,134} prepared pyrido[1,2-*b*][1,2]benzothiazines (Scheme 8): 1,2-benzothiazine **182** with isopropyl iodide and potassium carbonate resulted in spontaneous aldol cyclization of the intermediate enol ether **183** to 7,8-dihydro-8-hydroxy-11-isopropoxy 8-substituted pyrido[1,2-*b*][1,2]benzothiazin-10(9*H*)-one 5,5 dioxides (**184**). In sulfuric acid, dehydration and ether cleavage of **184** gave the corresponding unsaturated β -diketone **185**. Hydrogenation gave the saturated analogs **186**. An attempt to prepare **186** directly by base-catalyzed cyclization of **187** afforded a high yield of 2,3-dihydro-6*H*-oxepino [3,2-*c*][1,2]benzothiazin-5(4*H*)-one 7,7-dioxides (**188**) (Eq. 39).

¹³² C. R. Rasmussen, U.S. Patent 3,492,299 (1970) [CA 72, 79075 (1970)].

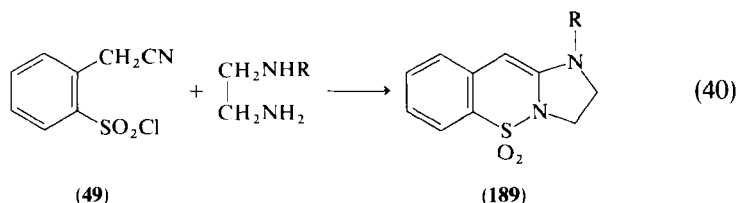
¹³³ H. Zinnes, R. A. Comes, and J. Shavel, *J. Med. Chem.* 10, 223 (1967).

¹³⁴ J. Shavel, and H. Zinnes, U.S. Patent 3,408,347 (1968) [CA 70, 68387 (1969)].



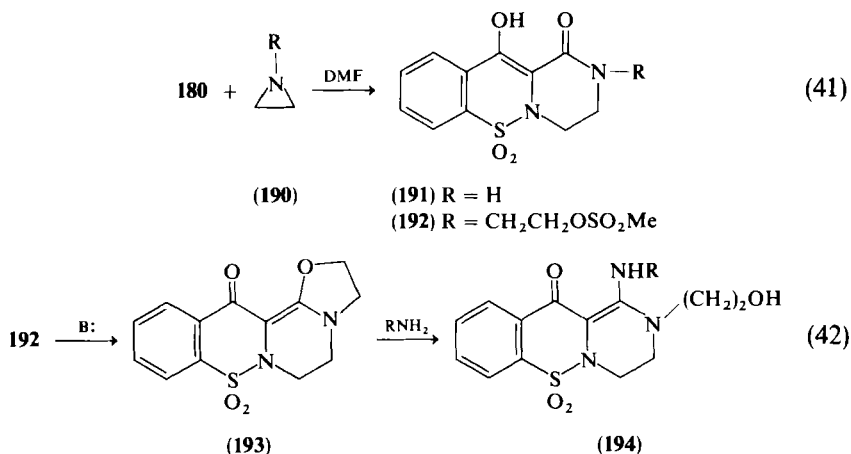
SCHEME 8

Kubo and co-workers¹³⁵ reacted 2-cyanomethylbenzenesulfonyl chloride (**49**) with ethylenediamines to afford 1-substituted-2,3-dihydroimidazo-[3,2-*b*][1,2]benzothiazine 5,5-dioxides (**189**) (Eq. 40). This is the only sequence in this section that does not use a preformed 1,2-benzothiazine as a starting material. The products are claimed to possess analgesic, anti-inflammatory, and antipyretic activities.¹³⁵

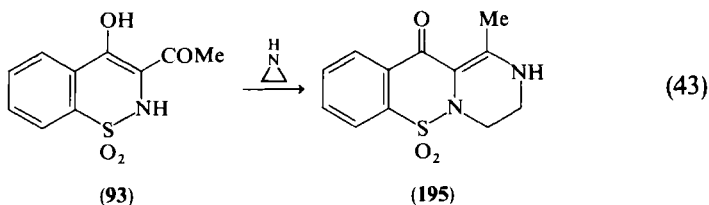


¹³⁵ K. Kubo, N. Ito, I. Soto, Y. Isomura, and H. Honma, Japanese Patent 79/22,399 (1979) [*CA* **91**, 5235 (1979)].

The versatile ester **180** with N-substituted aziridines (**190**) affords^{136,137} many 1,2,3,4,-tetrahydro-11-hydroxypyrazino[1,2-*b*][1,2]benzothiazin-1(2*H*)-one 6,6-dioxides (**191**) (Eq. 41). 1,2,3,4-Tetrahydro-11-hydroxy-2-(2-hydroxyethyl)pyrazino[1,2-*b*][1,2]benzothiazin-1(2*H*)-one 6,6-dioxide (**191**; R = CH₂CH₂OH), after conversion into the methanesulfonate **192**, was treated with base to give the tetracyclic system **193** (Eq. 42). Compound **193** can be isolated in the reaction of **192** with various nucleophiles. Thus, reaction of **192** or **193** with secondary amines and mercaptides produces **191** (R = CH₂CH₂NR¹R²) and **191** (R = CH₂CH₂SR), respectively. Reaction of **192** or **193** with primary amines gave **194** (Eq. 42).^{136,137}



Similar ring systems were prepared from 3-acetyl-4-hydroxy-2*H*-1,2-benzothiazine 1,1-dioxide (**93**) and ethylenimine (**190**; R = H)^{137,138} (Eq. 43) or ethylene dibromide (forming **95**).^{8,139} The ethylenimine reaction gave only



¹³⁶ C. R. Rasmussen, U.S. Patent 3,787,398 (1974) [CA **80**, 95985 (1974)]; U.S. Patent 3,787,401 (1974) [CA **80**, 83060 (1974)]; U.S. Patent 3,787,402 (1974) [CA **80**, 95988 (1974)]; U.S. Patent 3,787,403 (1974) [CA **80**, 95984 (1974)]; U.S. Patent 3,787,404 (1974) [CA **80**, 95999 (1974)].

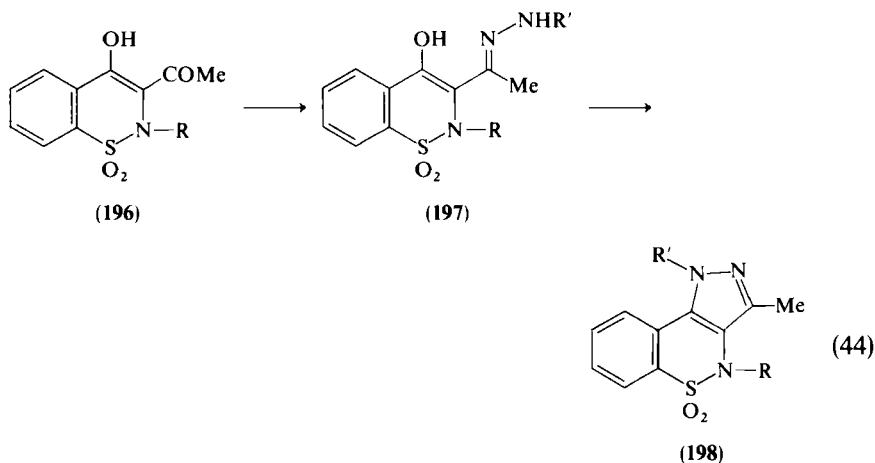
¹³⁷ C. R. Rasmussen and D. L. Shaw, *J. Org. Chem.* **39**, 1560 (1974).

¹³⁸ C. R. Rasmussen, U.S. Patent 3,787,399 (1974) [CA **80**, 83059 (1974)].

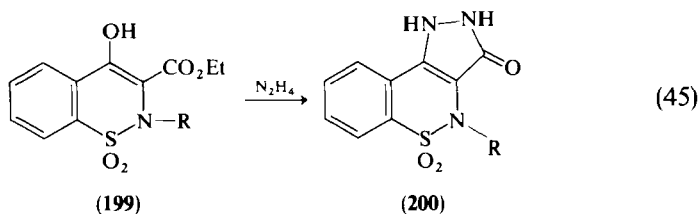
¹³⁹ C. R. Rasmussen, U.S. Patent 3,821,212 (1974) [CA **81**, 91546 (1974)].

a low yield of 3,4-dihydro-1-methylpyrazino[1,2-*b*][1,2]benzothiazine-11(2*H*)-one 6,6-dioxide (**195**). The preparation of the related tricycle (**98**) was previously discussed (Eq. 23).^{8,140}

The reaction of 3-benzoyl- (or 3-acetyl) -4-hydroxy-2*H*-1,2-benzothiazine 1,1-dioxide (**89**) with hydrazine to produce pyrazolo[4,3-*c*][1,2]benzothiazine 5,5-dioxide derivatives was discussed in Section II,B,1 (See Eq. 22). Steiner¹⁴¹ recently reacted 3-acetyl-1,2-benzothiazines (**196**) with alkyl-substituted hydrazines; the hydrazones (**197**) were usually not isolated but cyclized directly to 1-substituted-1,4-dihydro-3-methylpyrazolo[4,3-*c*][1,2]-benzothiazine 5,5-dioxides (**198**) (Eq. 44).



Similarly, Steiner¹⁴¹ prepared 1,2,3,4-tetrahydro-3-oxopyrazolo[4,3-*c*]-[1,2]benzothiazine 5,5-dioxide (**200**) from the ester **199** and hydrazine (Eq. 45).



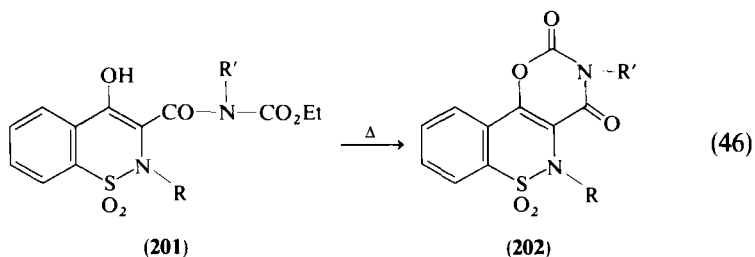
Rasmussen^{142,143} prepared the 2*H*,5*H*-1,3-oxazino [5,6-*c*][1,2]benzothiazine-2,4(3*H*)-dione 5,5-dioxide (**202**) by heating 1,2-benzothiazine derivative **201** (Eq. 46). Anti-inflammatory and antiarthritic activities were claimed for **202** ($\text{R}' = \text{aryl}$).¹⁴³

¹⁴⁰ C. R. Rasmussen, U.S. Patent 3,787,400 (1974) [*CA* **80**, 95987 (1974)].

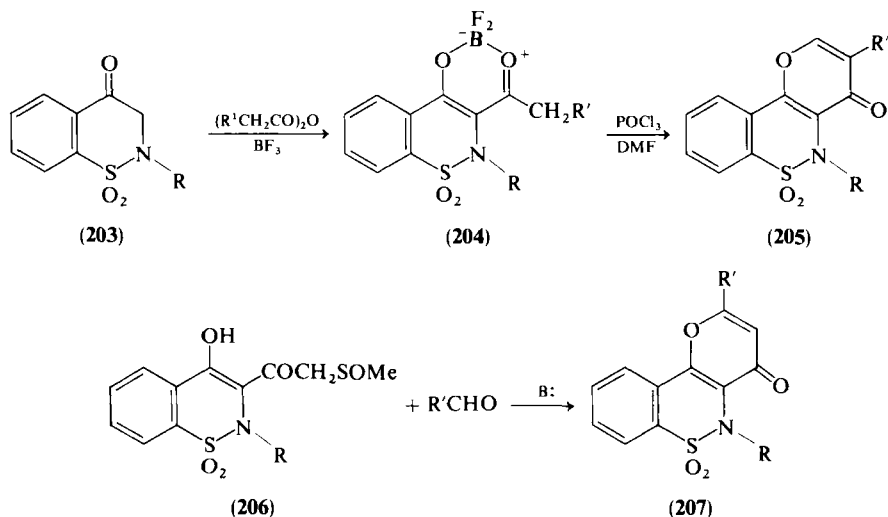
¹⁴¹ G. Steiner, *Justus Liebigs Ann. Chem.*, 643 (1978).

¹⁴² C. R. Rasmussen, U.S. Patent 3,492,298 (1970) [*CA* **72**, 66964 (1970)].

¹⁴³ C. R. Rasmussen, U.S. Patent 3,923,801 (1975) [*CA* **84**, 59521 (1976)].



Novel antisecretory and antiallergic pyrano[3,2-*c*][1,2]benzothiazine 6,6-dioxides (**205** and **207**) have been prepared by two processes (Scheme 9). In the first,¹⁴⁴ 2-alkyl-3,4-dihydro-2*H*-1,2-benzothiazin-4-one 1,1-dioxide (**203**), boron trifluoride etherate, and an acid anhydride afforded the isolable boron complex **204**. Reaction of **204** with the Vilsmeier reagent (POCl₃/DMF) gave, after hydrolysis, 3,5-disubstituted pyrano[3,2-*c*][1,2]benzothiazin-4(5*H*)-one 6,6-dioxides (**205**). The second route¹⁴⁵ gives a different substitution pattern in the pyrone ring. Thus, β -sulfinyl ketone **206**, when reacted with aldehydes under base catalysis, gave 2,5-disubstituted pyrano[3,2-*c*][1,2]benzothiazin-4(5*H*)-one 6,6-dioxides (**207**) (Scheme 9).

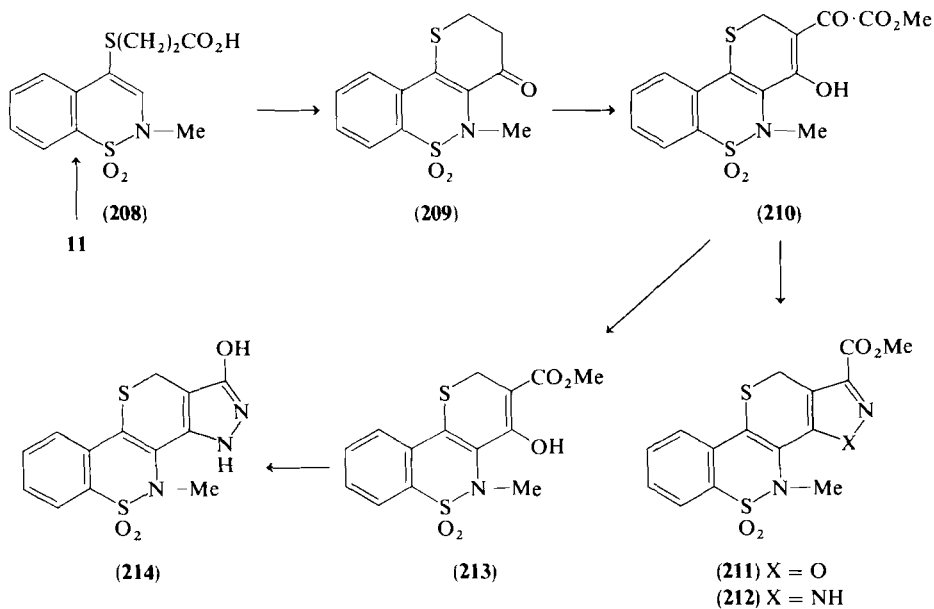


SCHEME 9

¹⁴⁴ D. Kaminsky, S. Klutchko, and M. von Strandtmann, U.S. Patent 3,855,216 (1974) [CA **82**, 112087 (1975)]; U.S. Patent 3,937,828 (1976) [CA **84**, 164807 (1976)]; see also D. Kaminsky, U.S. Patent 3,898,218 (1975) [CA **84**, 17388 (1976)]; U.S. Patent 3,966,716 (1976) [CA **85**, 177502 (1976)].

¹⁴⁵ M. von Strandtmann, S. Klutchko, M. P. Cohen, and J. Shavel, *J. Heterocycl. Chem.* **9**, 171 (1972); U.S. Patent 3,816,466 (1974).

In studies of heterocyclic steroid analogs, Fravolini and co-workers¹⁴⁶ prepared tri- and tetracyclic 1,2-benzothiazines (Scheme 10). 2-Methyl-2*H*-1,2-benzothiazin-4(3*H*)-one 1,1-dioxide (**11**) with thioglycolic acid gives intermediate **208**, cyclized by polyphosphoric acid to 5-methyl-4-oxo-2,3,4,5-tetrahydrothiopyrano[3,2-*c*][1,2]benzothiazine 6,6-dioxide (**209**). Condensation of **209** with dimethyl oxalate gave **210** in high yield. Heating **210** led to decarbonylation, affording the β -keto ester **213**. Reaction of **210** or **213** with hydrazine gave 4,11-dihydro-4-methyl-1-carbomethoxy-3*H*-pyrazolo[3',4'-4,5]thiopyrano[3,2-*c*][1,2]benzothiazine 5,5-dioxide (**212**) or 4,11-dihydro-4-methyl-1-hydroxy-3*H*-pyrazolo[3',4'-4,5]thiopyrano[3,2-*c*][1,2]benzothiazine 5,5-dioxide (**214**), respectively. Reaction of **210** with hydroxylamine in acetic acid yielded 4-methyl-1-carbomethoxy-4*H*,11*H*-isoxazolo[5',4'-4,5]thiopyrano[3,2-*c*][1,2]benzothiazine 5,5-dioxide (**211**).

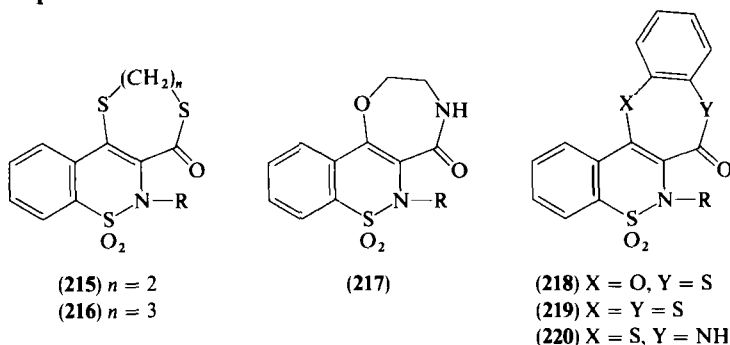


SCHEME 10

Steiner¹⁴¹ has also prepared heterocyclic derivatives in which a seven- or eight-membered ring is fused to the 3,4-position of the 1,2-benzothiazine molecule. Thus, reaction of ester **199** with 1,2-ethanedithiol, 1,3-propanedithiol, or ethanolamine gave **215**, **216**, or **217**, respectively. Similarly reaction of **199** with 2-mercaptophenol, 1,2-benzenedithiol, or *o*-aminophenol gave

¹⁴⁶ A. Fravolini, F. Schiaffella, and G. Strappaghetti, *J. Heterocycl. Chem.* **16**, 29 (1979).

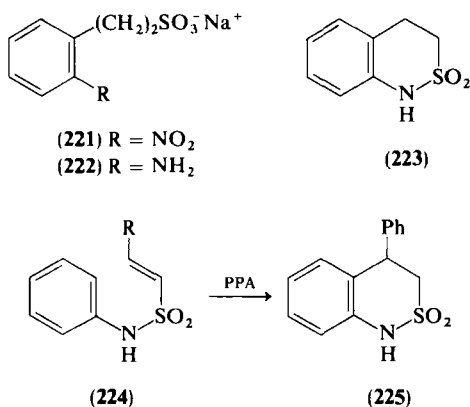
218, 219 or 220.¹⁴¹ Thioamide and amidine derivatives of **220** have also been reported.¹⁴¹



VI. 2,1-Benzothiazines

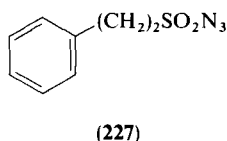
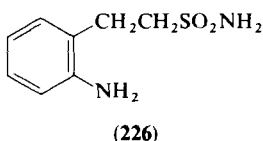
A. SYNTHESSES

Loev and Kormendy¹⁴⁷ first synthesized a 2,1-benzothiazine 2,2-dioxide by converting 2-(*o*-nitrophenyl)ethanesulfonyl chloride to the sulfonate salt **221** which was catalytically reduced to the amine **222**. Treatment of **222** with phosphorus pentachloride/acetyl chloride afforded 3,4-dihydro-1*H*-2,1-benzothiazine 2,2-dioxide (**223**). They also prepared 4-phenyl-3,4-dihydro-1*H*-2,1-benzothiazine 2,2-dioxide (**225**) by treating styrene sulfonanilide (**224**; $R = Ph$) with polyphosphoric acid. However, they were unable to cyclize the ethylene sulfonamide (**224**; $R = H$) to **223** using this route.¹⁴⁷

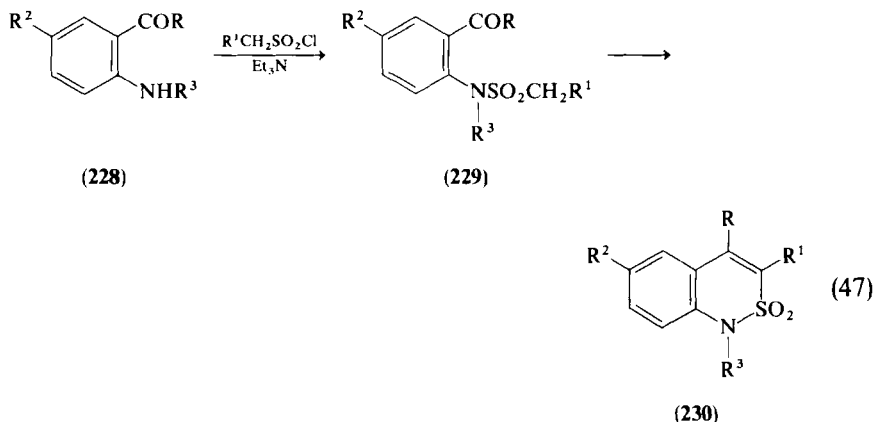


¹⁴⁷ B. Loev and M. F. Kormendy, *J. Org. Chem.* **30**, 3163 (1965); see also B. Loev, U.S. Patent 3,303,190 (1967) [*CA* **66**, P65486 (1967)].

The preparation of **223** by pyrolysis of 2-(*o*-aminophenyl)ethanesulfonamide (**226**) has also been reported.¹⁴⁸ Abramovitch and Holcomb¹⁴⁹ also prepared **223** together with uncyclized sulfonamides $\text{PhCH}_2\text{CH}_2\text{SO}_2\text{NHR}$ by thermolysis of β -phenethylsulfonyl azide **227**. The best yields of **223** (ca 30%) were obtained by using a solvent such as Freon-113 at 135°C for 36 hours.¹⁴⁹



Three groups independently synthesized early examples of the unsaturated 1*H*-2,1-benzothiazine 2,2-dioxides. Rossi and Pagani¹⁵⁰ reacted *o*-acylani-lines **228** with various sulfonyl chlorides to obtain *o*-acylsulfonamides **229**. Treatment of **229** with sodium ethoxide gave numerous 1*H*-2,1-benzothiazine 2,2-dioxides (**230**) containing substituents in the 1, 3, 4 and/or 6 positions (Eq. 47) in good to excellent yield; but the cyclization failed when both R^1 and R^3 were hydrogen. Rossi and Pagani¹⁵⁰ synthesized these latter derivatives of **230** by hydrolysis of ester **231**, which afforded the carboxylic acid **232**. Heating **232** with quinoline/copper powder gave **230** ($\text{R}^1 = \text{R}^3 = \text{H}$).



Sianesi and Redaelli¹⁵¹ also used the synthetic method of Eq. (47) to prepare substituted 1*H*-2,1-benzothiazine 2,2-dioxide derivatives. By starting

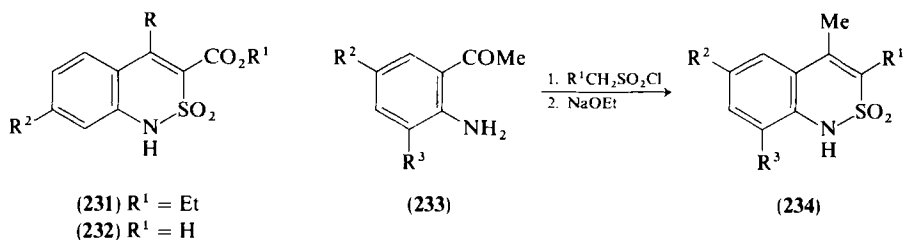
¹⁴⁸ E. Sianesi, G. Bonola, R. Pozzi, and R. Da Re, *Chem. Ber.* **104**, 1880 (1971).

¹⁴⁹ R. A. Abramovitch and W. D. Holcomb, *J. Am. Chem. Soc.* **97**, 676 (1975).

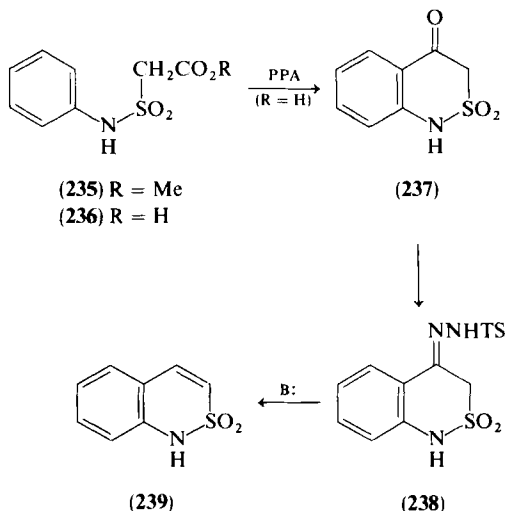
¹⁵⁰ S. Rossi and G. Pagani, *Ann. Chim. (Rome)* **56**, 728 (1966) [*CA* **65**, 10582 (1966)].

¹⁵¹ E. Sianesi and R. Redaelli, *Ann. Chim. (Rome)* **57**, 1426 (1967) [*CA* **69**, 2923 (1968)].

with *o*-aminoacetophenones (**233**) with substituents either ortho and/or para to the amino group, they made 1*H*-2,1-benzothiazines (**234**) with substituents in the 3, 6, and/or 8 position.



Loev and co-workers¹⁵² prepared the unsubstituted 1*H*-2,1-benzothiazine 2,2-dioxide (**239**) by the route of Scheme 11. Methyl chlorosulfonylacetate was converted into the sulfonanilide (**235**) by reaction with aniline. Hydrolysis of the ester group in **235** gave **236** which, with polyphosphoric acid, cyclized to 1*H*-2,1-benzothiazin-4-one (**237**). Spectral data indicated that **237** existed in the keto form. Ketone **237** was converted to the tosylhydrazone **238** which, by a Bamford–Stevens reaction, afforded **239** in good overall yield. The *N*-methyl analog of **239** was also prepared by the above reaction sequence using *N*-methylaniline.

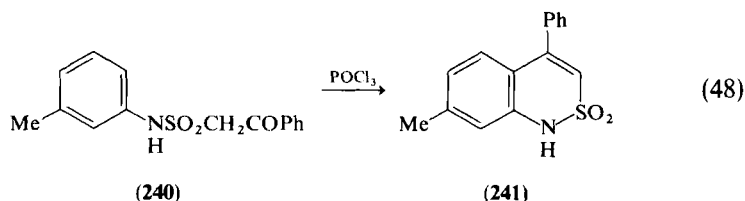


SCHEME 11

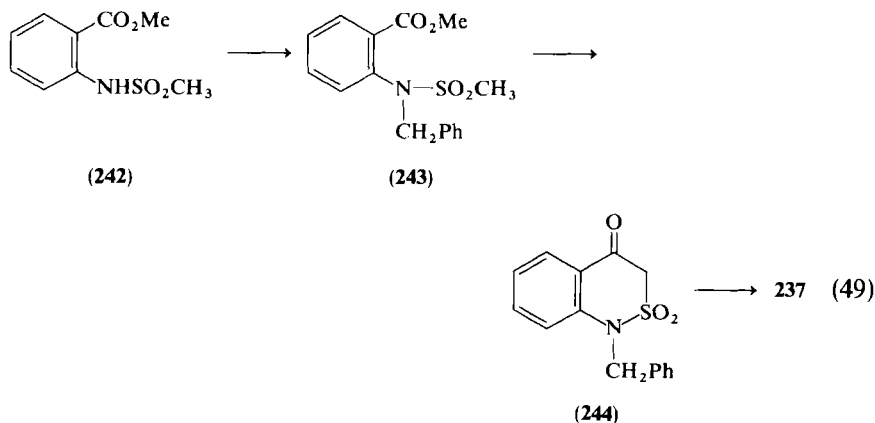
¹⁵² B. Loev, M. F. Kormendy, and K. M. Snader, *J. Org. Chem.* **31**, 3531 (1966).

Rossi and Pagani¹⁵³ independently prepared ketone **237** by the same route (Scheme 11). They then reduced **237** with sodium borohydride to an unstable alcohol which spontaneously dehydrated to the unsaturated 1*H*-2,1-benzothiazine 2,2-dioxide (**239**).

The same workers¹⁵³ extended a well-known carbostyryl synthesis based on cyclization of β -acylacetanilides to the corresponding β -acylsulfanilides. Thus, when heated in phosphorus oxychloride, sulfanilide **240** gave 4-phenyl-7-methyl-1*H*-2,1-benzothiazine 2,2-dioxide (**241**) (Eq. 48). However, the success of this reaction appears to be highly dependent on the substituents in the aniline starting material.¹⁵³



An improved synthesis of 3,4-dihydro-1*H*-2,1-benzothiazin-4-one 2,2-dioxide (**237**) was reported by Lombardino and Treadway.¹⁵⁴ *N*-Methylsulfonylanthranilic acid methyl ester (**242**) with benzyl bromide and sodium hydride gives the *N*-benzyl derivative (**243**) which directly cyclizes to 1-benzyl-4-oxo-3,4-dihydro-1*H*-2,1-benzothiazine 2,2-dioxide (**244**). Catalytic hydrogenation of **244** then gave **237** (Eq. 49). Lombardino¹⁵⁵ prepared



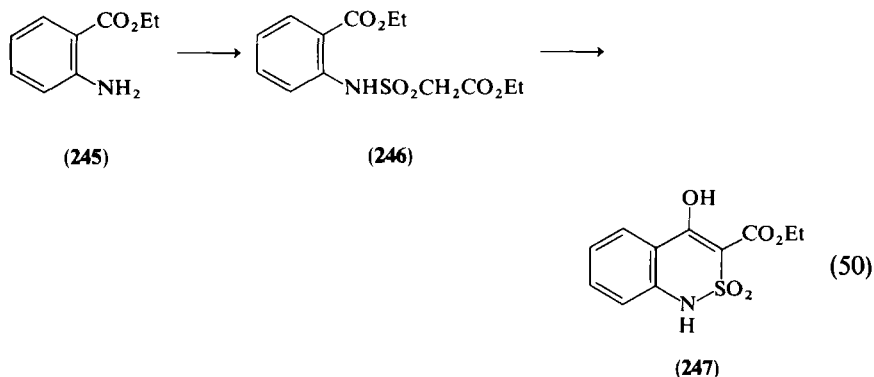
¹⁵³ S. Rossi and G. Pagani, *Ann. Chim. (Rome)* **56**, 741 (1966) [*CA* **65**, 10584 (1966)].

¹⁵⁴ J. G. Lombardino and N. Treadway, *Org. Prep. Proced. Int.* **3**, 33 (1971).

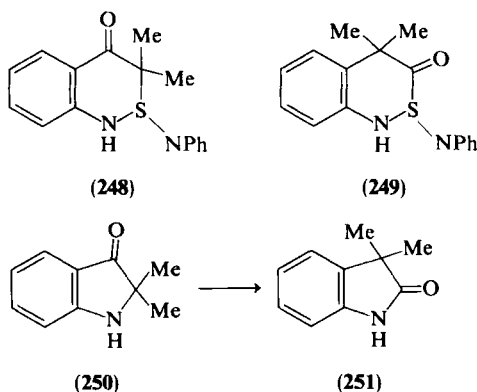
¹⁵⁵ J. G. Lombardino, *J. Heterocycl. Chem.* **9**, 315 (1972).

the *N*-methyl analog of **244** (95%) by cyclization of the *N*-methyl analog of **243**.

Nakanishi and Kobayashi¹⁵⁶ similarly prepared 3-ethoxycarbonyl-4-hydroxy-1*H*-2,1-benzothiazine 2,2-dioxide (**247**): ethyl anthranilate (**245**) gave the sulfonamide **246** which cyclized with base to afford **247** (Eq. 50).



Diphenyl sulfurdiiimide, $\text{PhN}=\text{S}=\text{NPh}$, and dimethyl ketene, $\text{Me}_2\text{C}=\text{C}=\text{O}$, gave a number of products,¹⁵⁷ one tentatively identified as 2-phenyl-imino-3,3-dimethyl-1*H*-2,1-benzothiazin-4-one (**248**). The isomeric **249** could not be completely excluded by the available spectral data. Chemical evidence

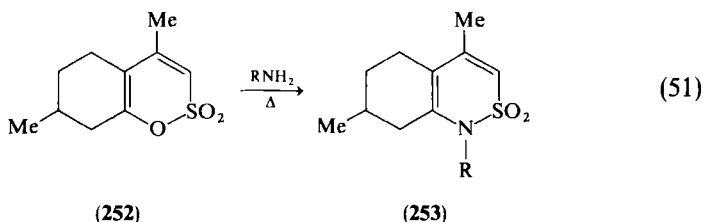


¹⁵⁶ M. Nakanishi and R. Kobayashi, Japanese Patent 71/22,152 (1971) [*CA* 75, 76820 (1971)]; Japanese Patent 71/22,150 (1971) [*CA* 75, 76818 (1971)].

¹⁵⁷ T. Minami, K. Yamataka, Y. Ohshiro, T. Agawa, N. Yasuoka, and N. Kasai, *J. Org. Chem.* 37, 3810 (1972).

initially favored **249** since reductive desulfurization with Raney nickel gave 3,3-dimethyloxindole (**251**) in high yield. However, since it was well-known that 2,2-disubstituted indoxyls rearrange to 3,3-disubstituted oxindoles, the original investigators¹⁵⁷ concluded that the probable initial reduction product **250** underwent Wagner–Meerwein rearrangements to give **251**. Therefore, they still favored structure **248** as the product of the initial cyclo-addition reaction.

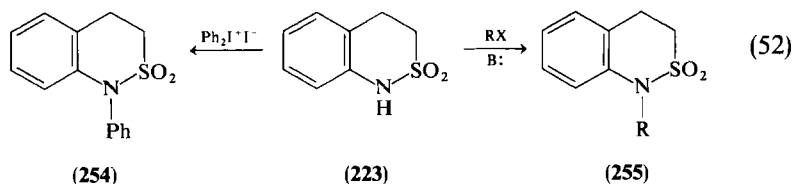
5,6,7,8-Tetrahydro-1*H*-2,1-benzothiazine 2,2-dioxides (**253**) have been prepared¹⁵⁸ by heating pulegone-1,4-sultone (**252**) with either aromatic or aliphatic amines (Eq. 51).



B. REACTIONS

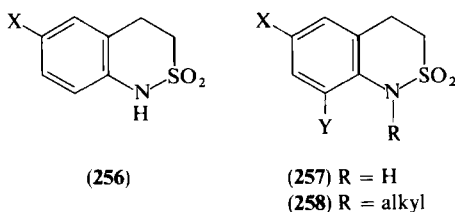
1. Reactions of 3,4-Dihydro-1*H*-2,1-benzothiazine 2,2-Dioxide (**223**)

Alkylation and arylation reactions of **223** have been studied by Loev and Kormendy¹⁴⁷ and by Sianesi and co-workers.¹⁴⁸ As expected, a variety of *N*-alkyl or *N*-aryl derivatives were obtained in high yield (Eq. 52).



The same groups have also examined electrophilic aromatic substitution reactions, using both **223** and **255** as substrates. Bromination of **223** gave the 6-bromo derivative (**256**; X = Br) or the 6,8-dibromo derivative (**257**; X = Y = Br) depending on the conditions.¹⁴⁷ Under all bromination conditions examined, compound **255** (R = alkyl) afforded only a 6-mono-brominated product **258** (X = Br, Y = H).

¹⁵⁸ B. Helferich, R. Dhein, K. Geist, H. Jünger, and D. Wiehle, *Justus Liebigs Ann. Chem.* **646**, 32 (1961).

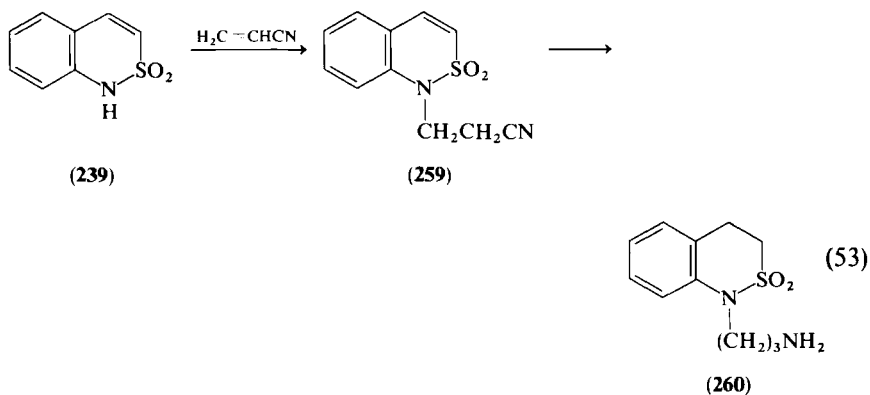


Nitration of **223** (65% nitric acid at 20°C) gave the 6,8-dinitro derivative **257** (X = Y = NO₂), whereas nitration at lower temperatures gave mixtures of mono-nitration products **256** (X = NO₂) and **257** (X = H, Y = NO₂). Nitration of **255** (R = alkyl) gave **258** (X = Y = NO₂).¹⁴⁸

Abramovitch and Holcomb¹⁴⁹ flash vacuum pyrolyzed **223** at 650°C to indoline (75%) and indole (7.7%). Only traces of these compounds were formed at 400°C. Loev and Kormendy¹⁴⁷ previously reported that **223** was thermally stable at 250°C.

2. Reactions of 1H-2,1-Benzothiazine 2,2-Dioxide (**239**)

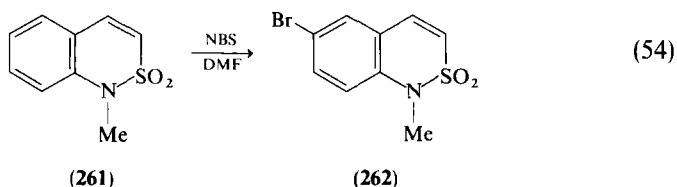
In general, reactions similar to those reported for 3,4-dihydro-1H-2,1-benzothiazine 2,2-dioxide (**223**) have also been examined with the unsaturated 1H-2,1-benzothiazine 2,2-dioxide (**239**). Alkylation^{151,152,159} or arylation,¹⁵⁹ for example, afforded *N*-alkyl or *N*-aryl derivatives in high yield. Loev¹⁶⁰ has also reported that 1-(γ-aminopropyl)-3,4-dihydro-1H-2,1-benzothiazine 2,2-dioxide (**260**) can be prepared from acrylonitrile and **239** by the Michael addition/reduction sequence pictured in Eq. (53).



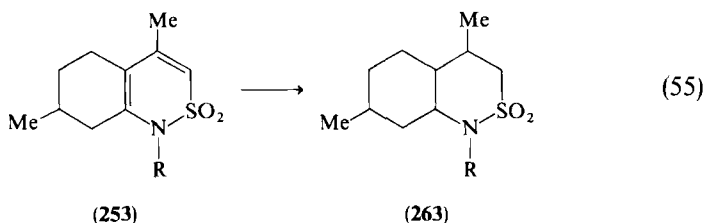
¹⁵⁹ B. Loev and K. M. Snader, *J. Heterocycl. Chem.* **4**, 407 (1967).

¹⁶⁰ B. Loev, U.S. Patent 3,303,189 (1967) [*CA* **66**, P65490 (1967)].

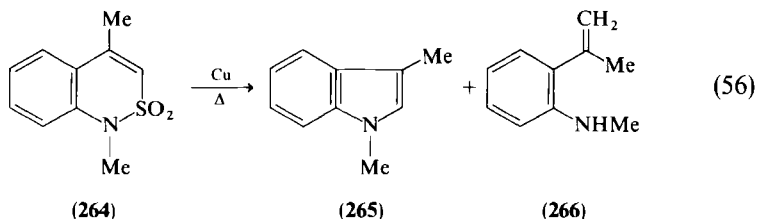
Bromination of **239**, even with limited amounts of the brominating reagent, afforded complex mixtures containing a tribromo derivative tentatively identified as 3(or 4),6,8-tribromo-1*H*-2,1-benzothiazine 2,2-dioxide. However, bromination of the *N*-methyl analog **261** using *N*-bromosuccinimide cleanly gave 6-bromo-1-methyl-1*H*-2,1-benzothiazine 2,2-dioxide (**262**) (Eq. 54).



Catalytic hydrogenation¹⁵⁹ (Pd/C) of 1*H*-2,1-benzothiazine 2,2-dioxide (**239**) gave the expected 3,4-dihydro derivative (**223**). Raney nickel reduction¹⁵⁸ of 5,6,7,8-tetrahydro-1*H*-2,1-benzothiazine 2,2-dioxide (**253**) afforded the completely saturated 2,1-benzothiazine **263** of undesigned stereochemistry (Eq. 55).

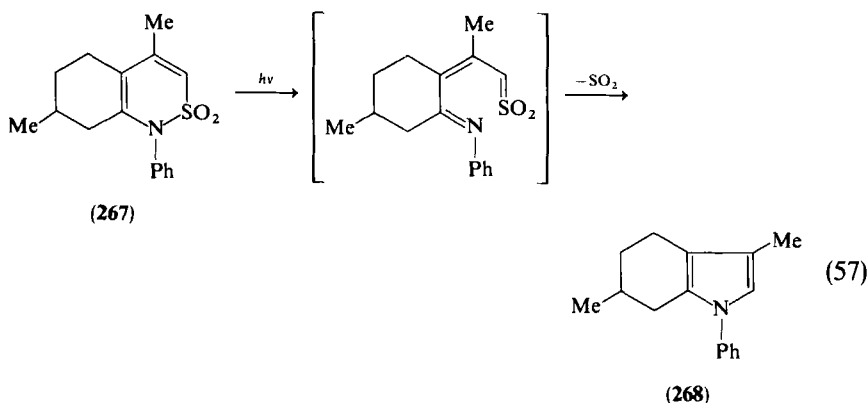


Two interesting sulfur extrusion reactions have been reported for derivatives of **239**. Rossi and Pagani,¹⁵⁰ upon heating 1,4-dimethyl-2,1-benzothiazine 2,2-dioxide (**264**) with copper powder at approximately 300°C, isolated the indole **265** and *o*-isopropenyl-*N*-methylaniline **266** (Eq. 56).



Durst and King¹⁶¹ obtained the pyrrole (**268**) by photolysis of 5,6,7,8-tetrahydro-4,7-dimethyl-1-phenyl-1*H*-2,1-benzothiazine 2,2-dioxide (**267**) (Eq. 57).

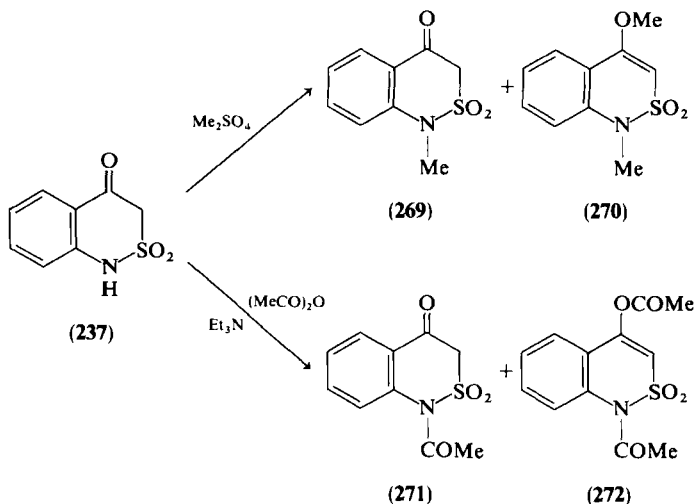
¹⁶¹ T. Durst and J. F. King, *Can. J. Chem.* **44**, 1869 (1966).



3. Reactions of 3,4-Dihydro-1H-2,1-benzothiazin-4-one 2,2-Dioxide (237)

Although spectral data showed no evidence of enolic character for **237**, the tautomeric nature of the carbonyl group was indicated by alkylation or acylation to the expected *N*-alkyl (**269**) and *N*-acyl (**271**) products which were always contaminated by *O*-alkylation (**270**) or *O*-acylation (**272**)¹⁶² (Scheme 12).

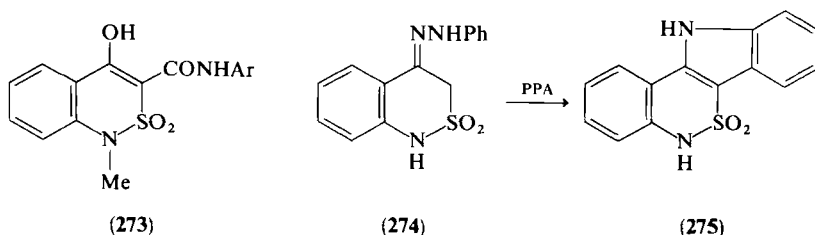
Lombardino¹⁵⁵ prepared 4-hydroxy-1-methyl-1H-2,1-benzothiazine-3-carboxanilides (**273**) by the base-catalyzed reaction of **269** with aryl isocya-



SCHEME 12

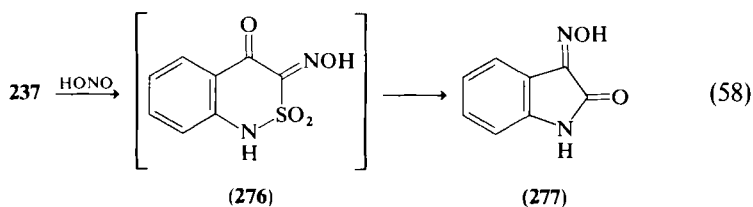
¹⁶² B. Loev and K. M. Snader, *J. Heterocycl. Chem.* **4**, 403 (1967).

nates. In this work **269** was prepared by an unambiguous synthesis (cf. Eq. 49) in order to avoid the problems associated with alkylation of **237**.



Compound **237** failed to form typical carbonyl derivatives, such as oximes, semicarbazones and enamines, under standard conditions.¹⁶² However, Loev^{162,163} was able to prepare a phenylhydrazone (**274**) from **237** which with polyphosphoric acid gave the novel tetracyclic indole **275**.

Treatment of ketone **237** with nitrous acid gave only the isatin β -oxime (**277**) by an unusual sulfur extrusion.¹⁶² The expected oxime **276** was postulated as an intermediate (Eq. 58).



VII. Conclusion

Literature reports on heterocyclic compounds containing a 1,2- or 2,1-benzothiazine ring have appeared in increasing numbers in recent years. This trend is likely to continue as a result of the anti-inflammatory activity of 4-hydroxy-2*H*-1,2-benzothiazine-3-carboxamide 1,1-dioxides (the "oxicams").

Note Added in Proof

More recent patents continue to report anti-inflammatory oxicams. Thus, Ferrini *et al.*¹⁶⁴ have found some *N*-(benzopyranyl)-4-hydroxy-2-alkyl-2*H*-1,2-benzothiazine-3-carboxamide 1,1-dioxides to be anti-inflammatory in animals.

¹⁶³ B. Loev, U.S. Patent 3,427,311 (1969) [*CA* **70**, 68391 (1969)].

¹⁶⁴ G. Ferrini, G. Haas, K. A. Jaeggi, and A. Rossi, European Patent 3-360 (1979).

After completion of this article, a 21-page review on all possible benzothiazinone dioxides, including 1,2- and 2,1-, as well as 1,3-, 2,3-, 1,4-, and 2,4-benzothiazinones, appeared.¹⁶⁵ By restricting their subject to 3-one and 4-one derivatives, these authors found 71 literature references to the 1,2- and 2,1-benzothiazinone dioxides. The present chapter discusses these references and a significantly larger number of patents and scientific articles dealing with all 2,1- and 1,2-benzothiazines.

ACKNOWLEDGMENT

The authors thank Dr. Beryl Dominy and Mr. John Hare of the Pfizer Technical Information Department for their help in computer-assisted searches of the scientific and patent literature and Mrs. Lynn Londregan, Mrs. Theresa D'Amico, and Mrs. Linda Neilan for typing this manuscript.

¹⁶⁵ P. Catsoulacos and C. Camoutsis, *J. Heterocycl. Chem.* **16**, 1503 (1979).

Isatoic Anhydrides and Their Uses in Heterocyclic Synthesis

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I. Introduction

A. HISTORICAL ASPECTS AND SCOPE OF THE REVIEW

When Friedländer and Wleügel¹ in 1883 reacted the so-called anthranil (2,1-benzisoxazole) (2) with ethyl chloroformate, they obtained a compound (C₈H₅NO₃) which they called anthranilic carboxylic acid. A year later,

¹ P. Friedländer and S. Wleügel, *Ber. Dtsch. Chem. Ges.* **16**, 2227 (1883).

Kolbe² in his last papers described a compound with the same formula, formed by oxidation of isatin (3) with CrO_3 , and called it "isatoic acid." Meyer³ proved the identity of both compounds, and Niementowski and Rozanski⁴ were the first to establish the correct formula (1) when they found a new synthesis from anthranilic acid (4) and ethyl chloroformate.

In 1899, Erdmann⁵ obtained the same compound in good yield from anthranilic acid and phosgene and suggested the name "isatoic anhydride." An alternative synthesis of isatoic anhydride [2*H*-3,1-benzoxazine-2,4(1*H*)-dione, subsequently abbreviated as IA] was found by Curtius and Semper⁶ from phthalic acid monoazide (5) via *o*-carboxyphenyl isocyanate. Similar rearrangements were discovered by Bredt and Hof⁷ [from potassium phthalimide (6)] and by Mohr⁸ [from phthalimide (7)] leading to IA via a Hoffmann reaction.

Initial investigations of IA* chemistry brought two types of reaction: ring opening to anthranilic acid derivatives^{1-3,6,7,9,10} and substitution in the aromatic nucleus.^{2,9,11}

No commonly available review of IA has yet been published (to our knowledge there are only chemical company brochures available¹²). The aim of this chapter is to cover the use of IA as a starting material for heterocyclic compounds. Other fields of application are not included [e.g., reactions leading only to open-chain anthranilic acid derivatives, use in the manufacture of agricultural chemicals, dyes, pigments, cross-linking agents and chain stoppers in resins and other uses in polymer and rubber chemistry, use as a modifier in protein and carbohydrate substrates (wool, paper, textiles), use as a petroleum additive (fuels and lubricants), use as a blowing agent for polymer foams, a flameproofing agent, and a corrosion inhibitor, use in metal finishing, for foods and beverages, soaps and detergents, perfumes, cosmetics, and use in medicines and pharmaceuticals.]

* Throughout this chapter, IA is used to denote the parent isatoic anhydride (1); IA's is used to denote IA and various benzene ring substituted analogs.

² H. Kolbe, *J. Prakt. Chem.* [2] **30**, 84, 124, 467 (1884).

³ E. von Meyer, *J. Prakt. Chem.* [2] **30**, 484 (1884); G. Schmidt, *ibid.* **36**, 370 (1889).

⁴ S. Niementowski and B. Rozanski, *Ber. Dtsch. Chem. Ges.* **22**, 1672 (1889).

⁵ E. Erdmann, *Ber. Dtsch. Chem. Ges.* **32**, 2159 (1899).

⁶ T. Curtius and A. Semper, *Ber. Dtsch. Chem. Ges.* **46**, 1162 (1913).

⁷ J. Bredt and H. Hof, *Ber. Dtsch. Chem. Ges.* **33**, 27 (1900).

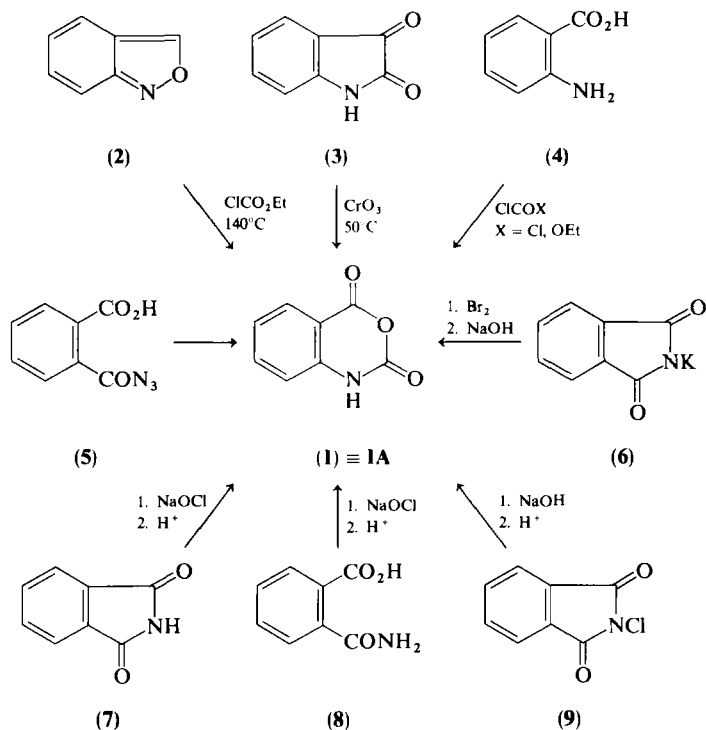
⁸ E. Mohr, *J. Prakt. Chem.* [2] **79**, 281 (1909).

⁹ W. Panatovic, *J. Prakt. Chem.* [2] **33**, 57 (1886).

¹⁰ E. Meyer and T. Bellmann, *J. Prakt. Chem.* [2] **33**, 18 (1886).

¹¹ R. Dorsch, *J. Prakt. Chem.* [2] **33**, 32 (1886).

¹² J. W. Long, ed., "Chemistry of Isatoic Anhydride," 3rd ed. Sherwin Williams Chemicals, 1975.



SCHEME 1

B. SYNTHESSES OF ISATOIC ANHYDRIDE AND RELATED COMPOUNDS

There are now three types of reaction commonly used for preparing IA.

1. Cyclization of anthranilic acid with carbonic acid derivatives (phosgene, ethyl chloroformate, see Scheme 1).^{4,5,13-26} The reaction mechanism and the by-products were studied by Peet and Sunder.²⁷

¹³ Merck & Co., Inc. (by F. C. Novello), U.S. Patent 2,910,488 (1959) [CA 54, 2271 (1960)].

¹⁴ E. C. Wagner and M. F. Fegley, *Org. Synth.* 27, 45 (1947); *Collect. Vol. III*, 488 (1956).

¹⁵ I. G. Farbenindustrie A. G. (by A. Ossenbeck and A. Tietze), German Patent 500, 916 (1928) [CA 24, 4793 (1930)]; British Patent 311, 336 (1928) [CA 24, 972 (1930)].

¹⁶ Farbenfabrik Bayer A. G. (by M. Gallus, G. Lorenz, and G. E. Nischke), Ger. Offen. 1,949,014 [CA 74, 76430 (1971)].

¹⁷ Parke, Davis and Co. (by R. A. Scherrer), French Patent M 3,007 (1965) [CA 62, 14684 (1965)]; Belgian Patent 637,515 (1964) [CA 63, 4307 (1966)]; Aktieselskabet Gea (by B. Alhede and K. Neuhold), South African Patent 68 04 065 (1969) [CA 72, 12408 (1970)].

2. Oxidation of isatin in glacial acetic acid with CrO_3 or peroxy carboxylic acids^{2,28-32} (see Scheme 1).

3. Rearrangement of phthalic acid derivatives. Treatment of phthalic anhydride with ammonia and NaOH leads to phthalamic acid (8), which rearranges with NaOCl to IA.^{33,34} The same result can be achieved starting with phthalimide (7)^{8,23,35-38} or *N*-chlorophthalimide (9).³⁹ Similar reactions starting with phthalic acid or anhydride via the azide (5) also give IA^{6,40,41} (see Scheme 1).

¹⁸ J. Martens, K. Praefcke, and U. Schulze, *Synthesis*, 532 (1976); R. V. Coombs, *J. Org. Chem.* **42**, 1812 (1977); J. H. Sellstedt, C. J. Guinosso, A. J. Begany, and M. Rosenthale, *J. Med. Chem.* **18**, 926 (1975).

¹⁹ G. M. Coppola, *J. Heterocycl. Chem.* **15**, 645 (1978).

²⁰ Hodogaya Chemical Co., Ltd. (by M. Suzuki, K. Yoshihara, and N. Igari), Japanese Patent 16,891 (1963) [*CA* **60**, 2858 (1964)].

²¹ BASF A. G., British Patent 783,067 (1957) [*CA* **52**, 2930 (1958)].

²² F. E. Sheibley, *J. Org. Chem.* **3**, 414 (1938).

²³ Hooker Chem. Corp. (by N. E. Boyer), *Tech. Apskats* **30**, 5 (1961); **31**, 13 (1961) [*CA* **59**, 1524, 1526 (1963)].

²⁴ G. E. Hardtmann, G. Koletar, and O. R. Pfister, *J. Heterocycl. Chem.* **12**, 565 (1975).

²⁵ T. H. Althuis, P. F. Moore, and H. J. Hess, *J. Med. Chem.* **22**, 44 (1979).

²⁶ D. L. Goldhamer, M. Onyszkewycz, and A. Wilson, *Tetrahedron Lett.*, 4077 (1968); K. Kurita, T. Matsumara, and Y. Iwakura, *J. Org. Chem.* **41**, 2070 (1976).

²⁷ N. P. Peet and S. Sunder, *J. Org. Chem.* **39**, 1931 (1974).

²⁸ Parke, Davis and Co. (by R. A. Scherrer), U.S. Patent 3,238,201 (1966) [*CA* **64**, 17614 (1966)].

²⁹ Searle, G. D. & Co. (by J. W. Cusic), U.S. Patent 3,509,149 (1970) [*CA* **73**, 3931 (1970)].

³⁰ H. Rupe and L. Keraten, *Helv. Chim. Acta* **9**, 578 (1926).

³¹ S. Inagaki, *J. Pharm. Soc. Jpn.* **58**, 946, 961 (1938); I. Nabih, and M. Abbasi, *J. Pharm. Sci.* **60** 1251 (1971); K. Geckeler and J. Metz, *Arch. Pharm.* **13**, 842 (1979); G. Reissenweber and D. Mangold, *Angew. Chem.* **92**, 196 (1980).

³² J. Wegmann and H. Dahn, *Helv. Chim. Acta* **29**, 415 (1946).

³³ BASF A. G. (by H. J. Quadbeck-Seeger and P. Tonne), Ger. Offen. 2,346,308 (1975) [*CA* **83**, 4335 (1975)]; Ger. Offen. 2,258,150 (1974) [*CA* **81**, 105532 (1974)].

³⁴ Farbenfabrik Bayer A. G., Fr. Demande 2,008,946 (1968) [*CA* **73**, 45177 (1970)].

³⁵ Maumee Chemical Co. (by D. R. Hill and W. A. Shire), U.S. Patent 3,324,119 (1967) [*CA* **68**, 2904 (1968)]; French Patent 1,500,957 (1967) [*CA* **70**, 11707 (1969)].

³⁶ Imp. Chem. Ind., Ltd. (by A. A. Kommander and I. Hodgkinson), British Patent 1,436,810 (1976) [*CA* **85**, 192397 (1976)].

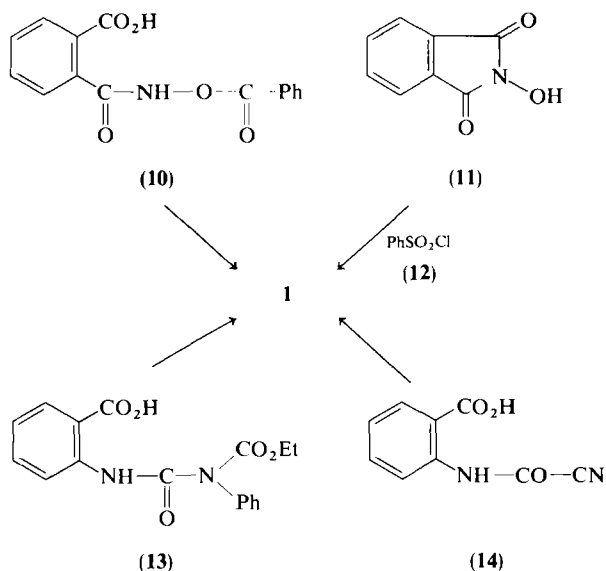
³⁷ BASF A. G. (by H. J. Sturm, H. Armbrust, and F. E. Kempter), Ger. Offen. 1,950,281 (1971) [*CA* **75**, 5495 (1971)].

³⁸ BASF A. G. (by H. J. Sturm, F. E. Kempter, and H. Armbrust), U.S. Patent 3,847,974 (1975) [*CA* **83**, 79255 (1975)].

³⁹ Sherwin Williams Co. (by L. C. Vacek), Ger. Offen. 2,230,374 (1973); Ger. Offen. 2,152,722 (1973); U.S. Patent 3,734,921 (1973); French Patent 2,153,766 (1973) [*CA* **78**, 159629 (1973); **79**, 32064, 42525, 92192 (1973)].

⁴⁰ G. Caronna, *Gazz. Chim. Ital.* **71**, 189 (1941).

⁴¹ G. Caronna, *Gazz. Chim. Ital.* **71**, 475 (1941).



SCHEME 2

Other methods of obtaining IA include oxidizing phthalamic acid (**8**) with $\text{Pb}(\text{OAc})_4$,^{42,43} thermally cyclizing the phthalamic acid derivative (**10**),⁴⁴ or treating *N*-hydroxyphthalimide (**11**) with benzenesulfonyl chloride (**12**)⁴⁵ (Schemes 1 and 2).

N-Substituted anthranilic acid derivatives are the starting materials of other preparations yielding IA. Heating of **13**,⁴⁶ **14**,^{47,48} or **15**,²⁸ or oxidizing **16**²⁸ gives various yields of IA. A 2-Isocyanatobenzoate (**17**), which is obtained either from phthalic anhydride and trimethylsilyl azide^{49a} or from anthranilic acid silyl ester,^{49b} is in equilibrium with *N*-trimethylsilyl-substituted IA,^{49a,49b} from which IA can be isolated by treatment with aqueous

⁴² A. L. J. Beckwith, Ger. Offen. 1,926,475 (1969) [CA 74, 76430 (1971)]; A. L. J. Beckwith and R. J. Hickman, *J. Chem. Soc. C*, 2756 (1968).

⁴³ Sherwin Williams Co. (by A. L. J. Beckwith), U.S. Patent 3,947,416 (1976) [CA 85, 33073 (1976)].

⁴⁴ C. D. Hurd, C. M. Buess, and L. Bauer, *J. Org. Chem.* **17**, 865 (1955).

⁴⁵ L. Bauer and S. V. Miarka, *J. Am. Chem. Soc.* **79**, 1983 (1957).

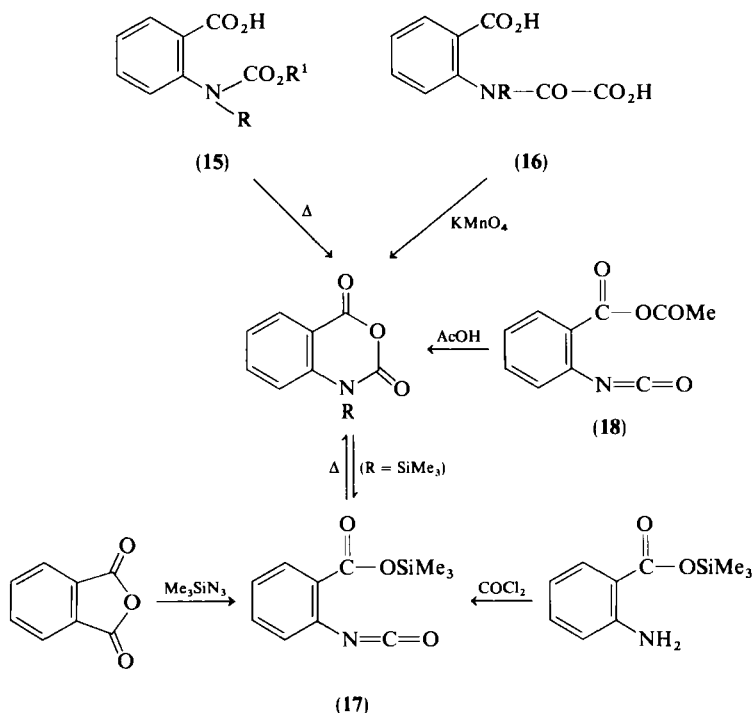
⁴⁶ S. Tohyama, M. Kurihara, and N. Yoda, *Bull. Chem. Soc. Jpn.* **43**, 1246 (1970).

⁴⁷ P. Karrer, G. H. Dieckmann, and W. T. Haller, *Helv. Chim. Acta* **7**, 1031 (1924).

⁴⁸ E. V. Crabtree, D. N. Cramer, and B. L. Murr, *J. Org. Chem.* **43**, 268 (1978).

^{49a} S. S. Washburne, W. R. Peterson, and D. A. Berman, *J. Org. Chem.* **37**, 1738 (1972).

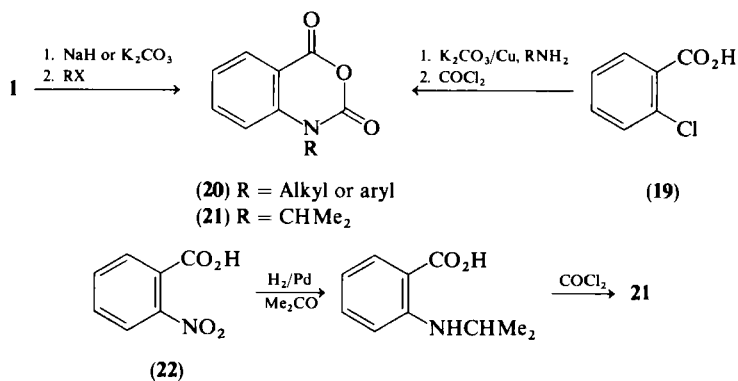
^{49b} G. Greber and H. R. Kricheldorf, *Angew. Chem.* **80**, 1029 (1968); H. R. Kricheldorf and G. Greber, *Chem. Ber.* **104**, 3131, 3168 (1971); V. R. Kozyukov, V. N. Mironova, and V. F. Mironov, *Zh. Obshch. Khim.* **49**, 784 (1979) [CA 91, 20592 (1979)].



SCHEME 3

ethanol.^{49a} Another method to obtain IA derives from the isocyanate **18**^{49c} (Schemes 2 and 3).

N-Substituted IA can be obtained by treating the unsubstituted IA (1) with NaH or K_2CO_3 and alkyl- or arylhalides (or tosylates).^{24,50} Reaction of *o*-



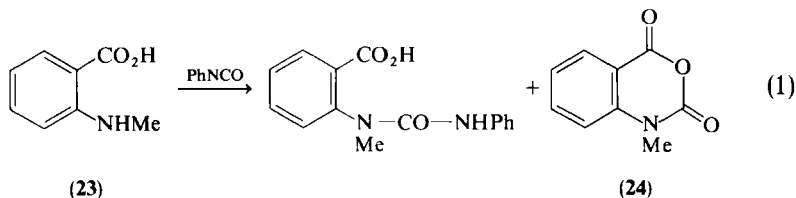
SCHEME 4

^{49c} L. Hoesch and A. S. Dreiding, *Helv. Chim. Acta* **58**, 980 (1975).

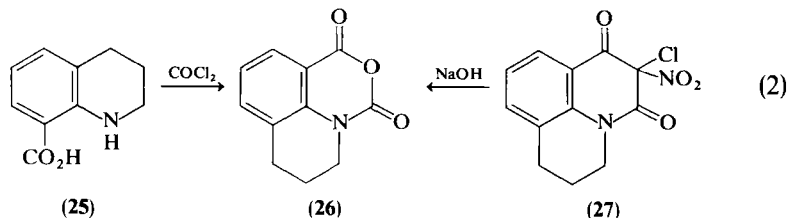
⁵⁰ R. W. Hall, F. C. Bernhardt, and C. F. Beam, *J. Heterocycl. Chem.* **15**, 495 (1978).

chlorobenzoic acid (**19**) with copper and primary amines and catalytic reduction of *o*-nitrobenzoic acid (**22**) in the presence of acetone, followed by ring closure with phosgene,²⁴ are other methods of obtaining N-substituted IA (**20**, and **21**) (Scheme 4).

N-Methyl IA (**24**), prepared from IA and diazomethane or dimethyl sulfate, is commercially available. This compound was isolated as a by-product of the reaction of **23** with phenyl isocyanate (Eq. 1).⁵¹



Usually, N-substituted IA's are synthesized by the action of phosgene on the corresponding N-substituted anthranilic acids, for example, the tricyclic derivative (**26**) was recently prepared in high yield from tetrahydroquinoline-8-carboxylic acid (**25**).¹⁹ An earlier preparation of **26** required a five-step synthesis via **27**⁵² (Eq. 2). (For the analogous synthesis of IA itself via the corresponding chloronitroquinoline derivative see Ref. 53).



Aza analogs of IA^{39,42,43,54,55} and polycondensed analogs⁵⁶ (**28**) can be prepared by the same procedures as shown in Scheme 5.

⁵¹ M. Kurihara and N. Yoda, *Bull. Chem. Soc. Jpn.* **39**, 1942 (1966); *Tetrahedron Lett.*, 2597 (1965).

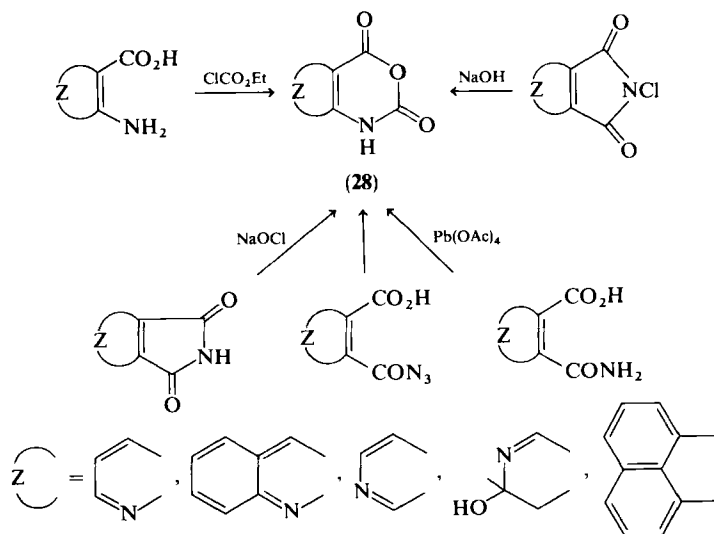
⁵² E. Ziegler and T. Kappe, *Monatsh. Chem.* **95**, 59 (1964).

⁵³ T. Kappe and E. Ziegler, *Monatsh. Chem.* **95**, 415 (1964).

⁵⁴ Sherwin Williams Co. (by G. F. Schlaudecker), U.S. Patent 3,622,573 (1971) [*CA* **76**, 46210 (1972)]; Sherwin Williams Co. (by L. C. Vacek), U.S. Patent 3,828,038 (1974) [*CA* **81**, 136171 (1974)]; Sherwin Williams Co. (by A. L. J. Beckwith), U.S. Patent 3,887,550 (1975) [*CA* **83**, 147504 (1975)].

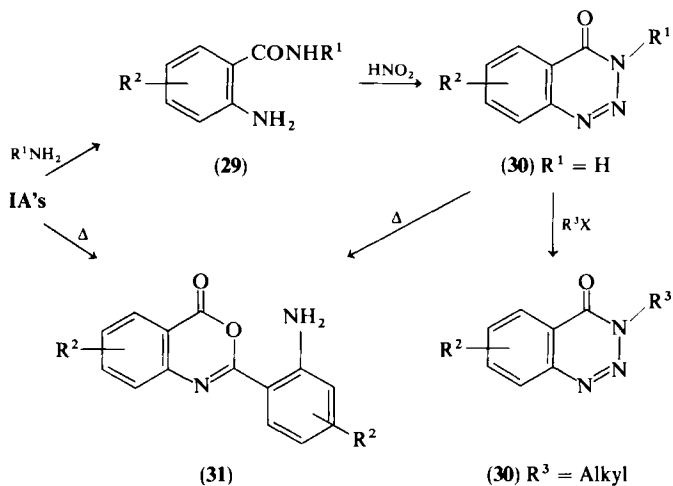
⁵⁵ C. D. Hurd and V. G. Bethune, *J. Org. Chem.* **35**, 1471 (1970); H. R. Kricheldorf, *Chem. Ber.* **105**, 3958 (1972); H. R. Kricheldorf, *Makromolek. Chem.* **173**, 13 (1973).

⁵⁶ D. A. Herold and R. D. Rieke, *J. Org. Chem.* **44**, 1359 (1979); J. M. Saa and M. P. Cava, *J. Org. Chem.* **43**, 1096 (1978); BASF A. G. (by F. Ebel and R. Randebrock), British Patent 719, 193 (1954) [*CA* **50**, 409 (1956)].



SCHEME 5

Reaction of anthranilic acid amides (29) with nitrous acid gives 4-benzotriazinones (30) which in many reactions behave in the same way as IA⁵⁷⁻⁶²;



SCHEME 6

⁵⁷ J. G. Archer, A. J. Baker, and R. K. Smalley, *J. Chem. Soc.*, 1169 (1973).

⁵⁸ S. M. Gadekar and E. Ross, *J. Org. Chem.* **26**, 613 (1961).

⁵⁹ H. Mehner, *J. Prakt. Chem.* [2] **63**, 241 (1901).

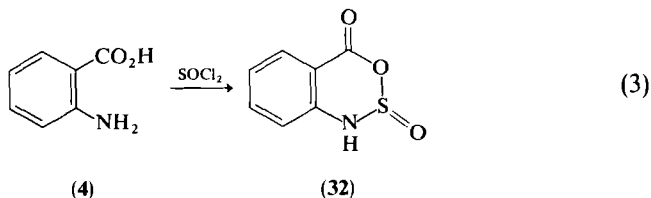
⁶⁰ A. Weddige and H. Finger, *J. Prakt. Chem.* [2] **35**, 262 (1887).

⁶¹ G. Heller and A. Siller, *J. Prakt. Chem.* [2] **116**, 9 (1927).

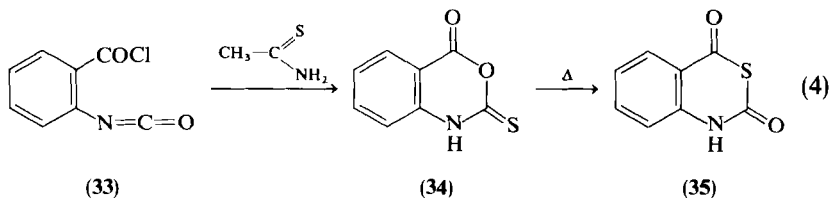
⁶² H. Finger, *J. Prakt. Chem.* [2] **37**, 431 (1888).

for instance, thermolysis of **30** yields the same compound (**31**) as does the heating of IA.⁵⁷ The formation of **31** as a by-product is observed in the reaction of IA with less reactive substrates (see also Section I,C).

Kametani has recently shown that 3,2,1-benzoxathiazin-4(1*H*)-one-2-oxide (**32**), the so-called "sulfinamide anhydride," which is isolated from the reaction of anthranilic acid and thionyl chloride⁶³ as an unstable oil (Eq. 3), undergoes reactions similar to IA but under milder conditions.⁶⁴⁻⁷⁰ This observation will probably have an important impact on IA chemistry.



The thio analog of IA (**34**) and its rearrangement product (**35**) can be prepared from 2-isocyanatobenzoyl chloride (**33**)⁷¹ and thioacetamide or from anthranilic acid (**4**) and thiophosgene⁷² (Eq. 4). The trithio compound **36**, which



has been synthesized from IA and phosphorus pentasulfide⁷³ (Eq. 5), reacts

⁶³ R. Graf and W. Langer, *J. Prakt. Chem.* [2] **148**, 161 (1937).

⁶⁴ T. Kametani, C. van Loc, T. Higa, M. Koizumi, M. Ihara, and K. Fukumoto, *Heterocycles* **4**, 1487 (1976).

⁶⁵ T. Kametani and K. Fukumoto, *Heterocycles* **7**, 615 (1977).

⁶⁶ T. Kametani, T. Ohsawa, M. Ihara, and K. Fukumoto, *Chem. Pharm. Bull.* **26**, 1922 (1978).

⁶⁷ T. Kametani, C. van Loc, T. Higa, M. Koizumi, M. Ihara, and K. Fukumoto, *J. Am. Chem. Soc.* **99**, 2306 (1977).

⁶⁸ T. Kametani, T. Higa, C. van Loc, M. Ihara, and K. Fukumoto, *Chem. Pharm. Bull.* **25**, 2735 (1977).

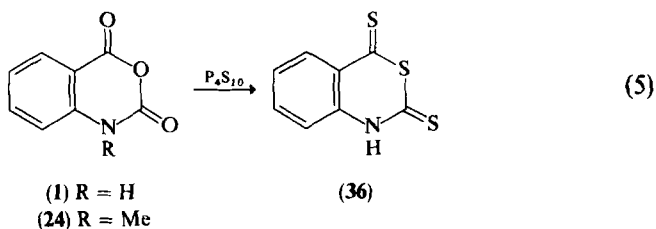
⁶⁹ T. Kametani, T. Higa, C. van Loc, M. Ihara, M. Koizumi, and K. Fukumoto, *J. Am. Chem. Soc.* **98**, 6186 (1976).

⁷⁰ T. Kametani, T. Higa, K. Fukumoto, and M. Koizumi, *Heterocycles* **4**, 23 (1976).

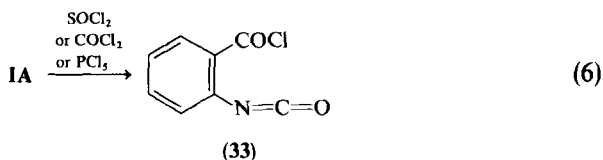
⁷¹ C. F. Beam, N. D. Heindel, M. Chun, and A. Stefanski, *J. Heterocycl. Chem.* **13**, 421 (1976).

⁷² J. R. Marshall, *J. Chem. Soc.*, 938 (1965); H. R. Kricheldorf, *Chem. Ber.* **104**, 3146, 3156 (1971).

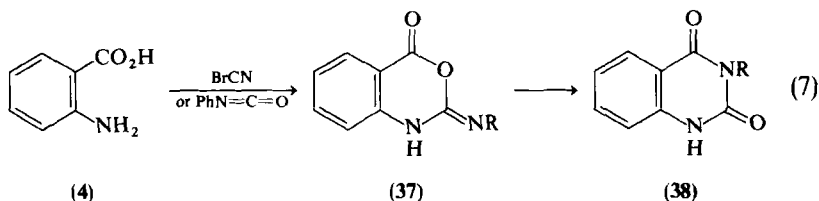
⁷³ G. Wagner and L. Rothe, *Pharmazie* **26**, 271 (1971); W. Walter, T. Fleck, J. Voss, and M. Gerwin, *Liebigs Ann. Chem.*, 275 (1975).



in a manner similar to IA.⁷⁴ The use of 2-Isocyanatobenzoyl chloride (33), an important and powerful intermediate in IA chemistry, results in the formation of heterocyclic compounds. It is prepared from IA with SOCl_2 , COCl_2 , or PCl_5 (Eq. 6).^{26,75-79} Anthranilic acid (4) and cyanogen bromide or phenyl



isocyanate react to give 37, imino analogs to IA, which undergo facile rearrangements to the quinazolininediones 38 (Eq. 7).^{51,80-82}



⁷⁴ S. Leistner, A. P. Giro, and G. Wagner, *Pharmazie* **33**, 185 (1978); **34**, 390 (1979); G. Wagner and L. Rothe, *Z. Chem.* **7**, 339 (1967); *Pharmazie* **25**, 595 (1970); S. Leistner and G. Wagner, *Z. Chem.* **13**, 428 (1973); S. Leistner and G. Wagner, *Pharmazie* **35**, 124 (1980); S. Leistner, G. Wagner, and T. Strohscheidt, *ibid.* **35**, 293 (1980); S. Leistner, G. Wagner, and K. Hentschel, *Z. Chem.* **20**, 143 (1980).

⁷⁵ Y. Iwakura, K. Uno, and S. Kang, *J. Org. Chem.* **31**, 142 (1966).

⁷⁶ N. P. Peet and S. Sunder, *J. Org. Chem.* **40**, 1909 (1975).

⁷⁷ H. Ulrich, B. Tucker, and A. A. R. Sayigh, *J. Org. Chem.* **32**, 4052 (1967).

⁷⁸ C. Vigne, M. Buti, C. Montginoul, E. Toreilles, and L. Giral, *J. Heterocycl. Chem.* **13**, 921 (1976).

⁷⁹ N. P. Peet, S. Sunder, and W. H. Braun, *J. Org. Chem.* **41**, 2728 (1976).

⁸⁰ K. Lempert and G. Doleschall, *Monatsh. Chem.* **95**, 950, 1083 (1964).

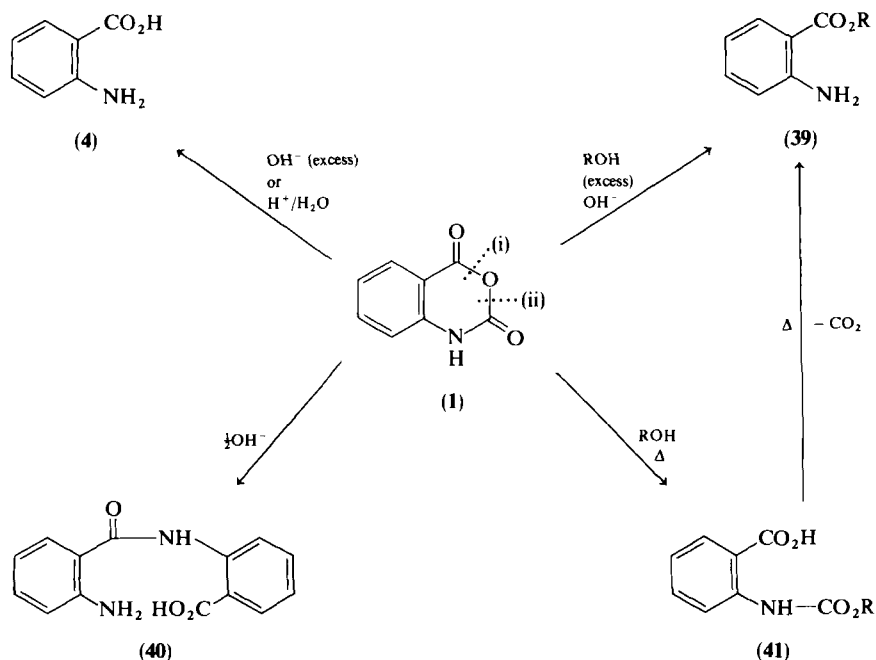
⁸¹ G. Doleschall and K. Lempert, *Acta Chim. Acad. Sci. Hung.* **48**, 77 (1966).

⁸² K. Lempert and G. Doleschall, *Tetrahedron Lett.* 781 (1963).

C. GENERAL MECHANISTIC AND THEORETICAL ASPECTS

The exceptional versatility of IA arises from the ease with which it enters into condensation and substitution reactions. The hetero ring is highly susceptible to cleavage [(i) or (ii)] and can be N-substituted with or without (see Scheme 4) ring opening.

Generally, the anthranilic carbonyl group (C-4) is more reactive than the isatoic carbonyl group (C-2). Steric hindrance and N-substitution sometimes reverse this trend. Refluxing IA in alkali or treatment with aqueous acids leads to quantitative decomposition to CO_2 and anthranilic acid (4).^{1,2,8} Reaction with one-half mole alkali or $\text{Ba}(\text{OH})_2$ forms anthraniloyl anthranilic acid (40),⁸ and the presence of alcohols and base catalysts gives the corresponding anthranilates (39).^{7,83-85} Uncatalyzed high-temperature esterification of the unsubstituted IA yields the isatoate 41,^{3,4,6,83,85} which can



SCHEME 7

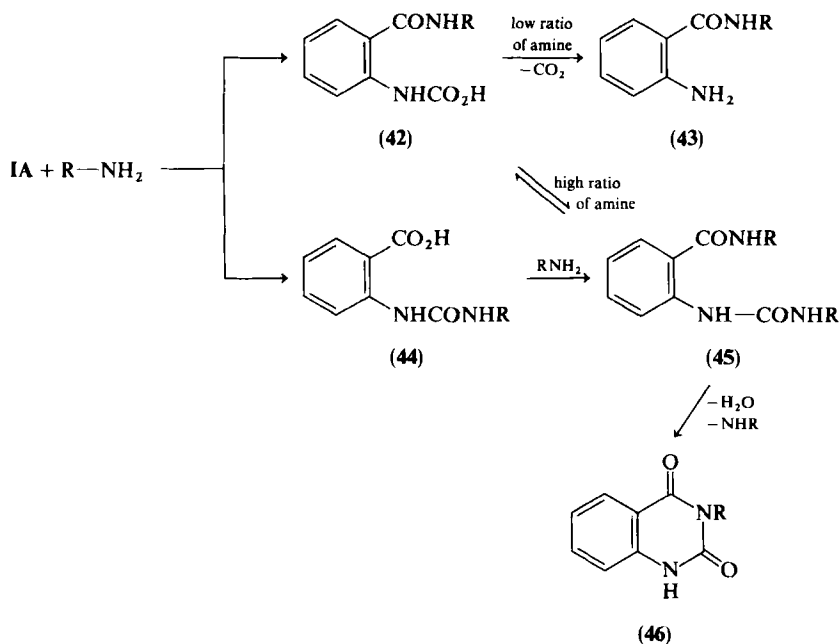
⁸³ R. P. Staiger and E. B. Miller, *J. Org. Chem.* **24**, 1214 (1959).

⁸⁴ J. Blahak, W. Meckel, and E. Müller, *Angew. Makromol. Chem.* **26**, 29 (1972).

⁸⁵ D. H. Heyman, *J. Heterocycl. Chem.* **15**, 1131 (1978).

be further converted to **39**.⁸⁵ The mechanism **1** → **41** → **39** involving 2-carboxyphenyl isocyanate as a reactive intermediate in the formation of **41** has been discussed⁸⁵ (Scheme 7).

The reaction with ammonia or primary amines in aqueous systems has been investigated repeatedly. Generally, two types of products are obtained during the reaction. The primary product is the ring-opened isatoic amide **42**, which reacts with loss of CO₂, favored by a low ratio of amine, to the anthranilic acid amide (**43**),^{2,6,10,86-88} while a high ratio of amine or bulky amines leads to isatoic diamides (**45**), which undergo facile cyclization to the quinazoline diones **36** by heating.^{86,89-93} The kinetics of the reaction of IA with *n*-butylamine show that the rate law for formation of **43** is zero order



SCHEME 8

⁸⁶ R. P. Staiger and E. C. Wagner, *J. Org. Chem.* **13**, 347 (1948).

⁸⁷ H. Finger, *J. Prakt. Chem.* [2] **48**, 92 (1893).

⁸⁸ Bayer A. G. (by K. W. Krebs and C. Metzger), Ger. Offen. 2,719,020 (1978) [*CA* **90**, 71928 (1979)].

⁸⁹ R. P. Staiger and E. C. Wagner, *J. Org. Chem.* **18**, 1427 (1953).

⁹⁰ F. R. Sheibley, *J. Org. Chem.* **3**, 415 (1938); **12**, 743 (1947); **17**, 221 (1952).

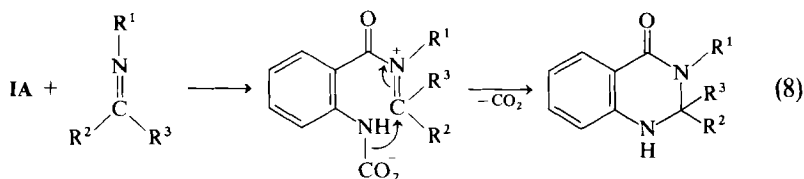
⁹¹ M. Covello, D. Dini, and F. De Simone, *Rend. Accad. Sci. Fis. Mat., Naples* **36**, 61 (1969) [*CA* **75**, 49011 (1971)].

⁹² R. H. Clark and E. C. Wagner, *J. Org. Chem.* **9**, 55 (1944).

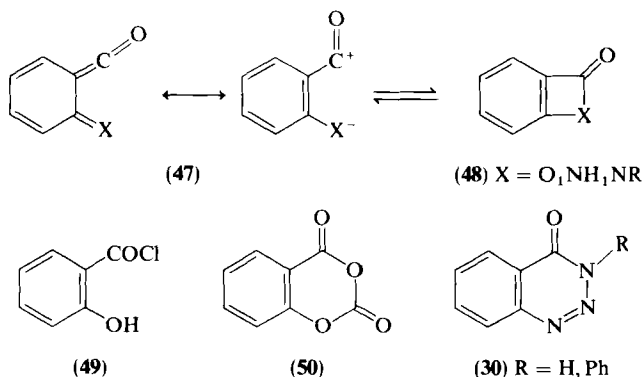
⁹³ R. L. McKee, M. K. McKee, and R. W. Bost, *J. Am. Chem. Soc.* **69**, 940 (1947).

in amine and first order in butylammonium ion; formation of **44** is first order in amine and zero order in butylammonium ion.⁹⁴ Under the same reaction conditions, *tert*-butylamine and IA formed only **44**.⁹⁴ N-Substituted IA's produce exclusively N-substituted **44**.^{83,94} Analogous results were obtained with esterifications⁸⁵ (Scheme 8).

With hydroxylamine, IA reacts to give the O-acylated product,^{10,95} while O-substituted hydroxylamines yield the anthranilic acid hydroxylamides⁹⁶ [cf. Eq. (14)]. Reaction of amides with IA results in the formation of quinazoline derivatives (see Section III,A), and the first reaction step has been proposed as acylation of the amide followed by decarboxylation and ring closure.^{92,97} A similar reaction mechanism⁹⁸ can be proposed for the reaction between IA and C=N double bond systems (Eq. 8) (see Section IV).



However, an alternative reaction mechanism⁹⁸ could be the cycloaddition of the iminoketene **47** ($\text{X} = \text{NH}, \text{NR}$) derived from IA by loss of CO_2 to the double bond system. The work of Ziegler and co-workers on salicyloyl



⁹⁴ J. F. Bunnett and M. B. Naff, *J. Am. Chem. Soc.* **88**, 4001 (1966).

⁹⁵ A. W. Scott and B. L. Wood, *J. Org. Chem.* **7**, 508 (1942).

⁹⁶ P. Mamalis, M. J. Rix, and A. A. Sarsfield, *J. Chem. Soc.*, 6278 (1965); H. Kohl and E. Wolf, *Liebigs Ann. Chem.* **766**, 106 (1972).

⁹⁷ T. Kappe, W. Steiger, and E. Ziegler, *Monatsh. Chem.* **98**, 214 (1967).

⁹⁸ E. Ziegler, T. Kappe, and W. Steiger, *Z. Naturforsch., Teil B* **20**, 812 (1965).

chloride (49),^{99,100} which was later extended to the cyclic carbonate (50),¹⁰¹ had suggested the analog intermediate (47; X = O) in corresponding reactions.¹⁰²

When heated in a high-boiling inert solvent, IA gave benzoxazinone 31 in 20% yield.^{57,103,104} The same compound was shown to result from photolysis and thermolysis of benzotriazinone (30; R = H); in both reactions the ketene imine 47 or its valence tautomeric β -lactam (48) were postulated as intermediates. Trapping reactions,¹⁰⁴⁻¹¹¹ dimerization or other internal stabilization^{57,103,104,107,108,110-120} of IA, 30, or related compounds confirm the assumption of the existence of these intermediates (47, 48).

IR spectra of IA and *N*-methyl IA (24) during thermal decomposition show bands of 1810–1830 cm^{-1} , which are in accordance with the proposed β -lactam 48.¹²¹ Analogous decomposition of 30 (R = phenyl) shows bands at 1830 cm^{-1} .^{106,108} The concentration of 47 in this thermolysis reaction was too small for detection in IR, but UV shows absorption at 575 nm, indicating the presence of 47.¹⁰⁶ Photochemical decomposition of phthaloyl peroxide yields 47 and 48 (X = O), showing IR frequencies at 1904 cm^{-1} (48) and 2139 cm^{-1} (47),¹⁰⁹ which could also be observed in the thermal decomposition of salicylic acid chloride (49) with 1930 cm^{-1} and 2070 cm^{-1} .¹²¹

⁹⁹ E. Ziegler and H. D. Hanus, *Monatsh. Chem.* **95**, 1053 (1964); **96**, 411 (1965).

¹⁰⁰ E. Ziegler, G. Kollenz, and T. Kappe, *Monatsh. Chem.* **99**, 804, 2024, 2167 (1968).

¹⁰¹ G. Kollenz and E. Ziegler, *Monatsh. Chem.* **101**, 97 (1970).

¹⁰² R. Gompper, *Angew. Chem.* **81**, 361 (1969); *Angew. Chem., Int. Ed. Engl.* **8**, 312 (1969).

¹⁰³ R. K. Smalley, H. Suschitzky, and E. M. Tanner, *Tetrahedron Lett.*, 3469 (1966).

¹⁰⁴ H. E. Crabtree, R. K. Smalley, and H. Suschitzky, *J. Chem. Soc. C*, 2730 (1968).

¹⁰⁵ H. Herlinger, *Angew. Chem.* **76**, 437 (1964); *Angew. Chem., Int. Ed. Engl.* **3**, 378 (1964).

¹⁰⁶ G. Ege, *Chem. Ber.* **101**, 3079 (1968); G. Ege and F. Pasedach, *ibid.*, 3089.

¹⁰⁷ G. Ege, *Angew. Chem.* **77**, 723 (1965); *Angew. Chem., Int. Ed. Engl.* **4**, 699 (1965); G. Ege and E. Beisiegel, *Angew. Chem.* **80**, 316 (1968); *Angew. Chem., Int. Ed. Engl.* **7**, 303 (1968); D. H. Hey, C. W. Rees, and A. R. Todd, *Chem. Ind. (London)*, 1332 (1962).

¹⁰⁸ A. W. Murray and K. Vaughan, *J. Chem. Soc. C*, 2070 (1970).

¹⁰⁹ O. L. Chapman, C. L. McIntosh, J. Pacansky, G. V. Calder, and G. Orr, *J. Am. Chem. Soc.* **95**, 4061 (1973).

¹¹⁰ A. T. Fannings and T. Roberts, *Tetrahedron Lett.*, 805 (1971).

¹¹¹ A. T. Fannings, G. R. Bickford, and T. D. Roberts, *J. Am. Chem. Soc.* **94**, 8505 (1972).

¹¹² T. McC. Paterson, R. K. Smalley, and H. Suschitzky, *Synthesis*, 187 (1975).

¹¹³ D. H. Hey, C. W. Rees, and A. R. Todd, *J. Chem. Soc. C*, 1028 (1968).

¹¹⁴ P. Ahern, T. Navratil, and K. Vaughan, *Tetrahedron Lett.*, 4547 (1973).

¹¹⁵ P. T. Ahern, H. Fong, and K. Vaughan, *Can. J. Chem.* **54**, 290 (1976).

¹¹⁶ A. J. Barker and R. K. Smalley, *Tetrahedron Lett.*, 4629 (1971).

¹¹⁷ E. M. Burgess and G. Milne, *Tetrahedron Lett.*, 93 (1966).

¹¹⁸ J. Adamson, D. L. Forster, T. L. Gilchrist, and C. W. Rees, *J. Chem. Soc. C*, 981 (1971).

¹¹⁹ C. T. Chen and C. J. Hsu, *Bull. Inst. Chem., Acad. Sin.* **14**, 57 (1967) [*CA* **69**, 35639 (1968)].

¹²⁰ American Cyanamid Co. (by G. R. Allen and R. F. R. Church), South African Patent 7,100,512 (1971) [*CA* **76**, 140237 (1972)].

¹²¹ E. Ziegler and H. Sterk, *Monatsh. Chem.* **99**, 1958 (1968).

In the light of these results, IA could react in two ways: (1) formation of the iminoketene (or β -lactam) by loss of CO_2 followed by $[4 + 2]$ -cycloaddition or (2) acylating the reaction partner in the first step with the anthranilic acid carbonyl group and cyclizing with loss of CO_2 as the second step. The mechanism in a particular case is largely dependent on the substrate used and the reaction conditions. Azomethines and heterocumulenes seem to undergo cycloaddition reactions in modest yields,⁹⁸ while a stepwise mechanism occurs faster and with better yields⁹⁷ with amides, thioamides, and related compounds. Analogous findings were reported with the "sulfonamide anhydride" (32),⁶⁴⁻⁷⁰ where a cycloaddition is presumed, but a stepwise mechanism could not be ruled out.

II. Formation of Anthranilic Acid Amides and Hydrazides and Further Reaction to Heterocycles

A. REACTION OF AMIDES WITH CARBONYL COMPOUNDS

1. Carboxylic Acid Derivatives

Formation of anthranilic acid amides (43) from IA is an established reaction (Section I,C), and Clark and Wagner⁹² isolated the quinazoline 51 from IA via 43 by ring closure with orthoformate. Analogous reactions were carried out with N-substituted IA's,¹²²⁻¹²⁵ primary amines,¹²⁶⁻¹²⁹ and formic acid derivatives, yielding 52 ($\text{R}^3 = \text{H}$). Ring closure with other carboxylic acid derivatives produce 52 ($\text{R}^3 = \text{alkyl, aryl}$)¹³⁰⁻¹³⁴; substitution of both nitrogens of 43 gives 53.¹³⁵ Reduction of anthranilamide (43) followed by ring

¹²² B. R. Baker, R. E. Schaub, J. P. Joseph, F. J. McEvoy, and H. J. Williams, *J. Org. Chem.* **17**, 164 (1952).

¹²³ Mead Johnson & Co. (by H. S. Scarborough and J. L. Minielli), U.S. Patent 3,119,824 (1964) [*CA* **60**, 9293 (1964)].

¹²⁴ M. K. McKee, R. L. McKee, and R. W. Bost, *J. Am. Chem. Soc.* **69**, 184 (1947).

¹²⁵ M. Vincent, J. C. Poignant, and G. Remond, *J. Med. Chem.* **14**, 714 (1971).

¹²⁶ Ciba Ltd. (by S. Janiak), Ger. Offen. 1,908,097 (1969) [*CA* **71**, 12448 (1969)].

¹²⁷ B. R. Baker, M. V. Querry, A. F. Kadish, and J. H. Williams, *J. Org. Chem.* **17**, 35 (1952).

¹²⁸ S. Johnne and B. Jung, *Pharmazie* **33**, 299 (1978).

¹²⁹ S. Johnne, M. Süsse, and B. Jung, *Pharmazie* **33**, 821 (1978).

¹³⁰ T. Hisano, M. Ichikawa, A. Nakagawa, and M. Tsuji, *Chem. Pharm. Bull.* **23**, 1910 (1975); K. Muraoka, M. Ichikawa, and T. Hisano, *Yakugaku Zasshi* **100**, 375 (1980).

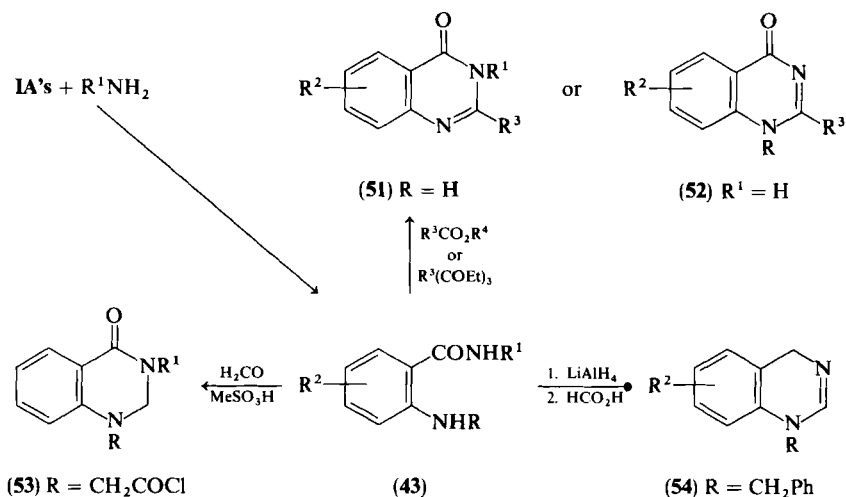
¹³¹ S. Hayayo, H. J. Havers, W. G. Stryker, and E. Hong, *J. Med. Chem.* **12**, 936 (1969).

¹³² I. M. Heilbron, F. N. Kitchen, E. B. Parks, and G. D. Sutton, *J. Chem. Soc.* **127**, 2167 (1925).

¹³³ T. Hisano, M. Ichikawa, G. Kito, and T. Nishi, *Chem. Pharm. Bull.* **20**, 2575 (1972).

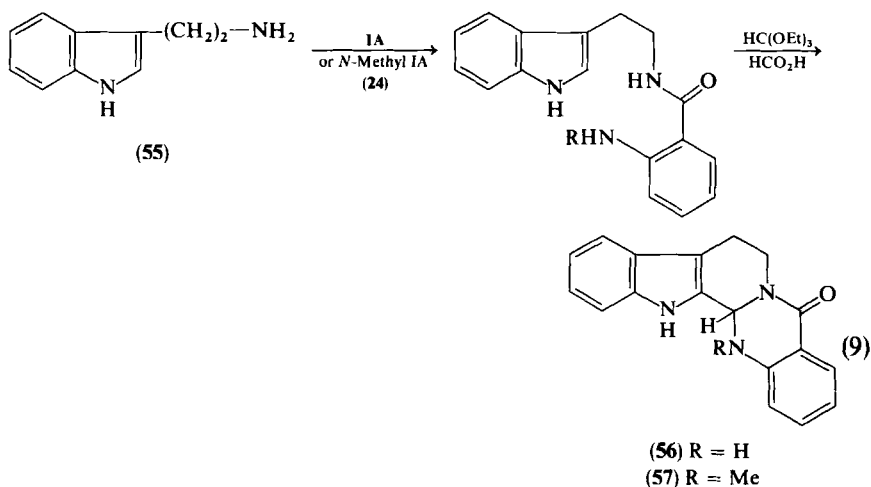
¹³⁴ G. Doleschall and K. Lempert, *Tetrahedron* **25**, 2539 (1969).

¹³⁵ L. Bonola, M. J. Magistretti, I. Setnikar, and E. Massarani, *Eur. J. Med. Chem.—Chim. Ther.* **9**, 639 (1974).



SCHEME 9

closure with formic acid leads to **54**¹³⁶ (Scheme 9). Using tryptamine (**55**) as the primary amine, ring closure takes place to form the alkaloids 3,14-dihydrorutecarpine (**56**) with IA¹³⁷ or evodiamine (**57**) with *N*-methyl IA (**24**) (Eq. 9).¹³⁸ Recently, these reactions were repeated with "sulfinamide anhydride" (**32**).^{64-67,69,70}

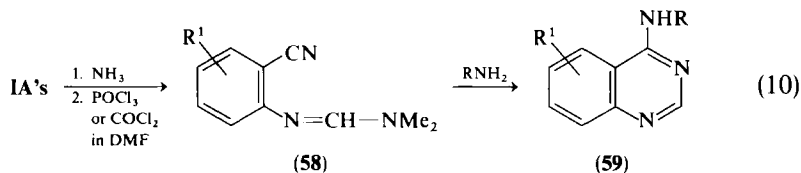


¹³⁶ W. L. F. Amarego, *J. Chem. Soc.*, 2697 (1961).

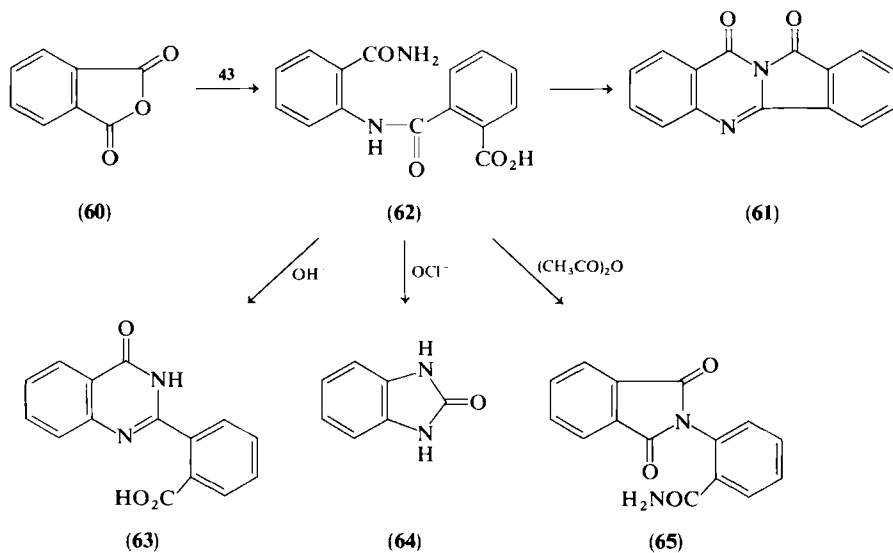
¹³⁷ K. Horvath-Dora and O. Clauder, *Acta Chim. Acad. Sci. Hung.* **84**, 93 (1975); **72**, 221 (1972); T. Kamikado, S. Murakoshi, and S. Tamura, *Agric. Biol. Chem.* **42**, 1515 (1978).

¹³⁸ Y. Asahina and T. Ohta, *Ber. Dtsch. Chem. Ges.* **61**, 319 (1928).

4-Aminoquinazolines (**59**) are obtained either conventionally by treating **51** (see Scheme 9) with PCl_5 and amine¹²⁴ or by reacting **IA** with ammonia and POCl_3 ¹³⁹ or phosgene¹⁴⁰ in DMF to give the formamidine **58**, which is then cyclized by heating with ammonia or primary amines to produce **59**¹³⁹ (Eq. 10). Reaction of phthalic anhydride with anthranilamide (**43**) forms 2-



carbamoylphthalanilic acid (**62**), which can be converted to the quinazolone **63** by treatment with sodium hydroxide¹⁴¹; reaction with hypohalite yields benzimidazolone (**64**)¹⁴¹; with acetic anhydride the phthalimide **65** was obtained.^{141,142} Thermolysis of **62** leads to the condensed quinazolone **61**¹⁴² (Scheme 10).



SCHEME 10

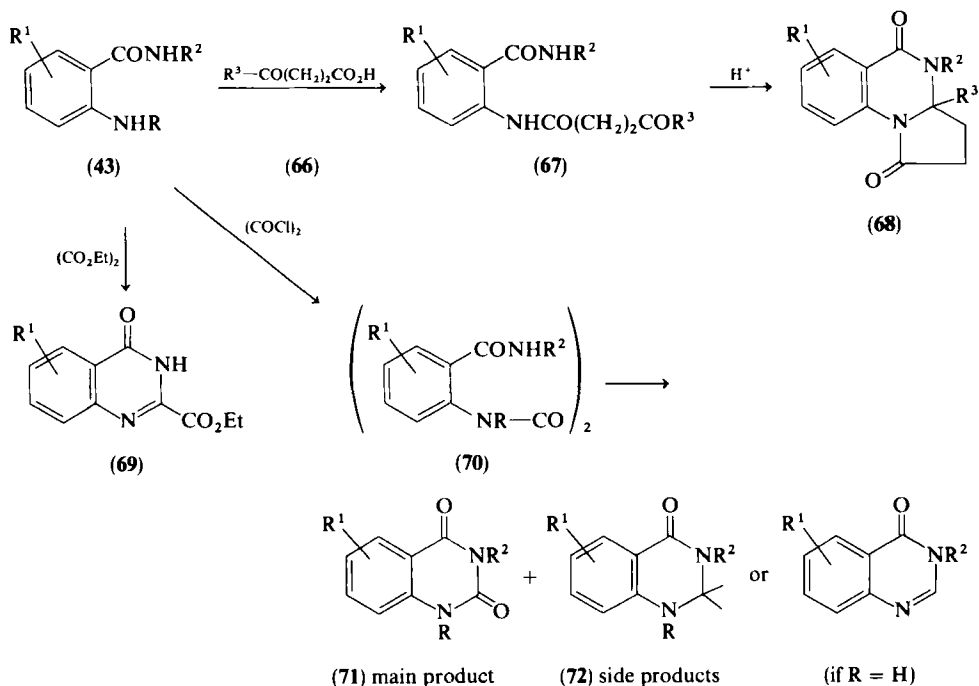
¹³⁹ C. H. Foster and E. U. Elam, *J. Org. Chem.* **41**, 2646 (1976); Eastman Kodak Co. (by C. H. Foster), U.S. Patent 3,985,749 (1976) [*CA* **86**, 43733 (1977)].

¹⁴⁰ BASF A. G. (by D. Schneider and H. Scheuermann), Ger. Offen. 2,628,055 (1978) [*CA* **88**, 104955 (1978)].

¹⁴¹ D. A. Heyman, *J. Heterocycl. Chem.* **15**, 573 (1978).

¹⁴² M. Kurihara, *J. Org. Chem.* **34**, 2123 (1969).

γ -Ketocarboxylic acids (**66**) react with anthranilamides (**43**) and acid catalysts to give, via acylated anthranilamides (**67**), pyrroloquinazolones **68**.^{143a} Oxalyl ester and **43** produce the quinoline carboxylate **69**.²⁵ With oxalyl chloride in the first step the oxanilide **70** is obtained which, upon thermolysis, gives mainly the quinazolidinedione **71**, with quinazolones **72**^{143b} as side products (Scheme 11). Addition of **43** to acetylenic dicarboxylate (**73**) forms the



SCHEME 11

primary adduct **74**, which undergoes ring closure on treatment with alcoholate yielding the quinazolone **75**^{144,145}; first observations interpreted in terms of a seven-membered ring system¹⁴⁶ have been corrected^{144,145} (Eq. 11).

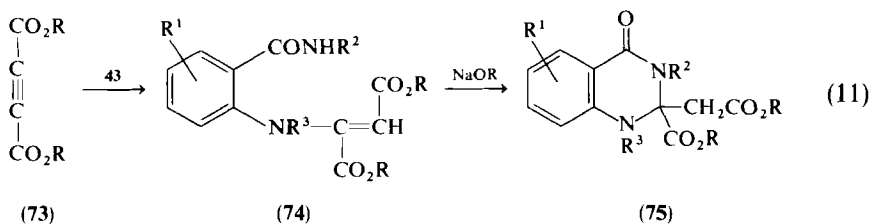
^{143a} C. S. Rao, A. D. Pandya, P. N. Mody, and M. P. Dave, *Indian J. Chem., Sect. B* **14**, 705 (1976).

^{143b} J. Gilbert, D. Rousselle, *C. R. Acad. Sci., Ser. C* **279**, 159 (1974).

¹⁴⁴ N. D. Heindel and L. A. Schaeffer, *J. Org. Chem.* **35**, 2445 (1970).

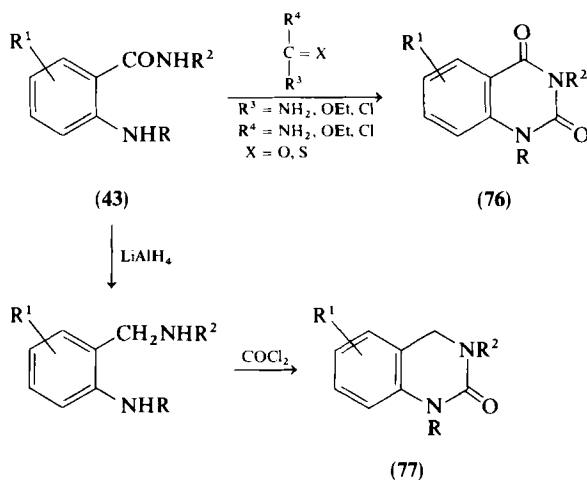
¹⁴⁵ T. F. Lemke, H. W. Snady, and N. D. Heindel, *J. Org. Chem.* **37**, 2337 (1972).

¹⁴⁶ N. D. Heindel, V. B. Fish, and T. F. Lemke, *J. Org. Chem.* **33**, 3997 (1968).



2. Carbonic Acid Derivatives

Urea, urethane, thiourea, and anthranilamide (43) furnish the corresponding oxo- or thioquinazolones (76)^{92,147}; ethyl chloroformate, thiophosgene, and phosgene react in the same manner.^{39,148-151} Reduction of the anthranilic acid carbonyl group with LiAlH_4 followed by cyclization with phosgene yields the quinazoline (77)¹⁵² (Scheme 12). Aryl and alkyl isocyanates and



SCHEME 12

¹⁴⁷ S. Toyoshima, K. Shimada, S. Hamano, and T. Ogo, *J. Pharm. Soc. Jpn.* **85**, 502 (1965).

¹⁴⁸ Casella Farbwerke Mainkur A. G. (by R. Beyerle and A. Stachel), Ger. Offen. 1,934,037 (1971) [*CA* **74**, 88029 (1971)].

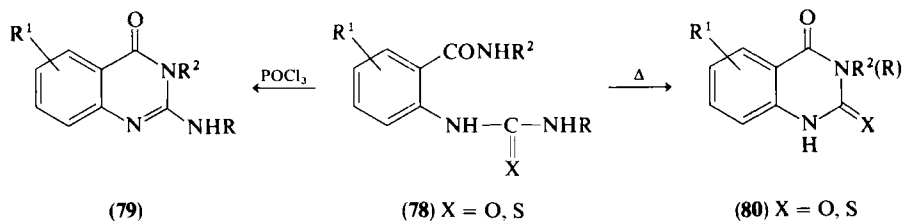
¹⁴⁹ Parke, Davis and Co. (by R. F. Parcell), Ger. Offen. 2,342,028 (1974) [*CA* **80**, 146, 190 (1974)].

¹⁵⁰ R. L. Jacobs, *J. Heterocycl. Chem.* **7**, 1337 (1970).

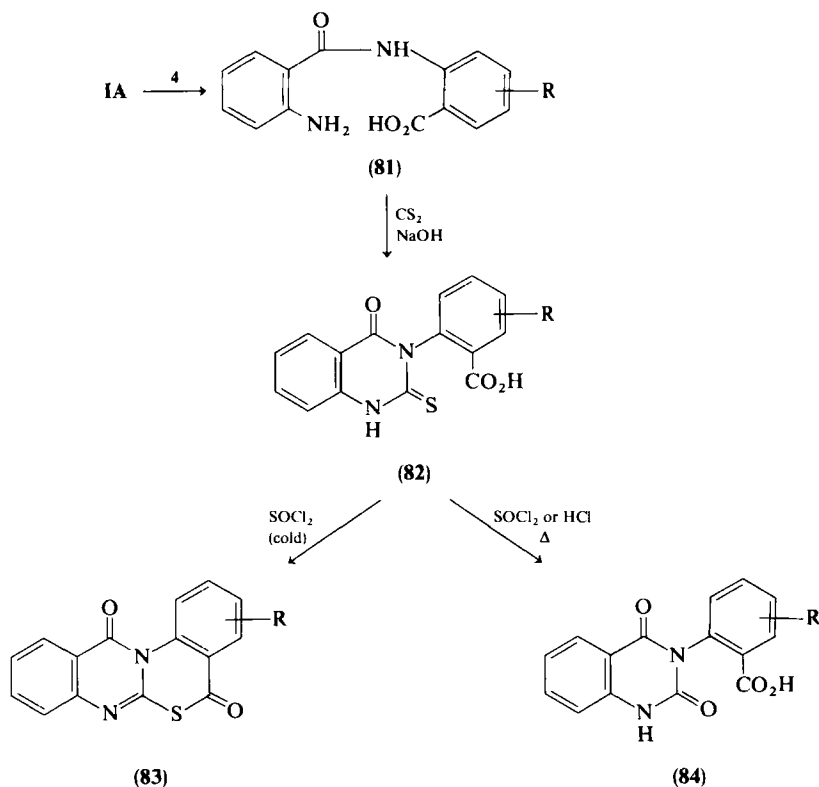
¹⁵¹ S. Hayayo, H. J. Havera, W. G. Stryker, T. J. Leipzig, R. A. Kulp, and H. E. Hartzler, *J. Med. Chem.* **8**, 807 (1965).

¹⁵² Searle, G. D. & Co. (by J. W. Cusic and W. E. Coyne), U.S. Patent 3,509,149 (1970) [*CA* **73**, 3931 (1970)].

isothiocyanates react with anthranilamides (43) to give uramidobenzamides (isatoic diamides) (78), which cyclize to quinazolones 79 when treated with POCl_3 .¹⁵³ Heating of 78 produces the quinazolines 80¹⁵⁴ (Scheme 13). The compounds 78 and 80 ($\text{X} = \text{O}$) were also obtained by reaction of IA with amines only (see Section I,C, Scheme 8, 45 \rightarrow 46). Anthraniloyl anthranilic



SCHEME 13



SCHEME 14

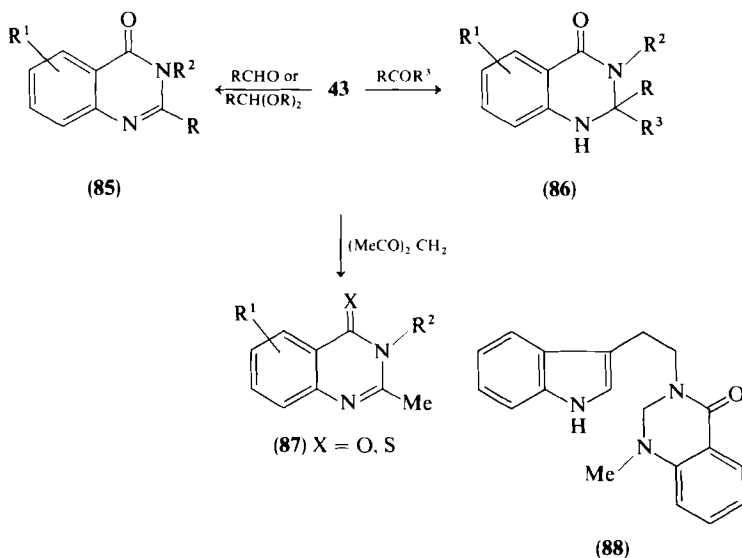
¹⁵³ W. Dymec and B. Lucka-Sobstel, *Diss. Pharm.* **17**, 195 (1965) [*CA* **63**, 16347 (1965)].

¹⁵⁴ A. Singh and B. M. Bhandari, *Indian J. Chem., Sect. B* **14**, 67 (1976).

acid (**81**) resulting from **1A** and anthranilic acid (**4**), gives with carbon disulfide the thioquinazolone **82**, which reacts with cold thionyl chloride yielding the quinazolinobenzothiazinone (**83**); with hot thionyl chloride or HCl the thio group of **82** is only converted to a carbonyl group and **84** is obtained¹⁵⁵ (Scheme 14).

3. Aldehydes, Ketones, and Heteroanalogs

Anthranilamides (**43**) and aldehydes (or their acetals) react when heated^{156,157} or oxidized¹³⁰ to give quinazolones **85**. The alkaloid dihydro-isoevodiamine (**88**) was obtained by the same sequence of reactions as evodiamine (**57**) [cf. Eq. (9)], using formaldehyde instead of formic acid.¹⁵⁸ Ketones give the corresponding 2,2-disubstituted quinazolones (**86**),¹⁵⁹ while diketones such as acetylacetone lead in an acid catalyzed reaction with anthranilamides (**43**) or thioanthranilamides to quinazolones of type **87**, which are methaqualone analogs¹⁶⁰ (Scheme 15).



SCHEME 15

¹⁵⁵ S. M. Singh, S. Kaur, and A. N. Kaushal, *J. Indian Chem. Soc.* **53**, 382 (1976).

¹⁵⁶ Pennwalt Corp. (by B. V. Shetty), U.S. Patent 3,761,480 (1973) [*CA* **79**, 137186 (1973)].

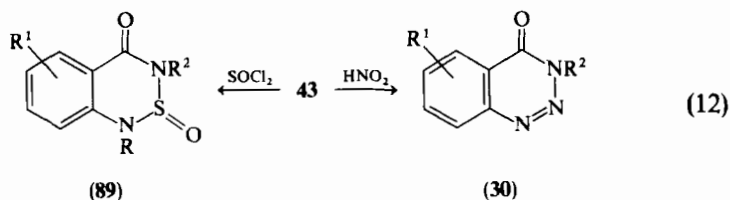
¹⁵⁷ H. L. Yale and M. Kalkstein, *J. Med. Chem.* **10**, 334 (1967).

¹⁵⁸ B. Danieli and G. Palmisano, *Gazz. Chim. Ital.* **105**, 99 (1975).

¹⁵⁹ H. L. Yale, *J. Heterocycl. Chem.* **14**, 1357 (1977); N. Hirose, S. Kuriyama, S. Sohda, K. Sakaguchi, and H. Yamamoto, *Chem. Pharm. Bull.* **21**, 1005 (1973).

¹⁶⁰ M. S. Manhas, S. G. Amin, and V. V. Rao, *Synthesis*, 309 (1977).

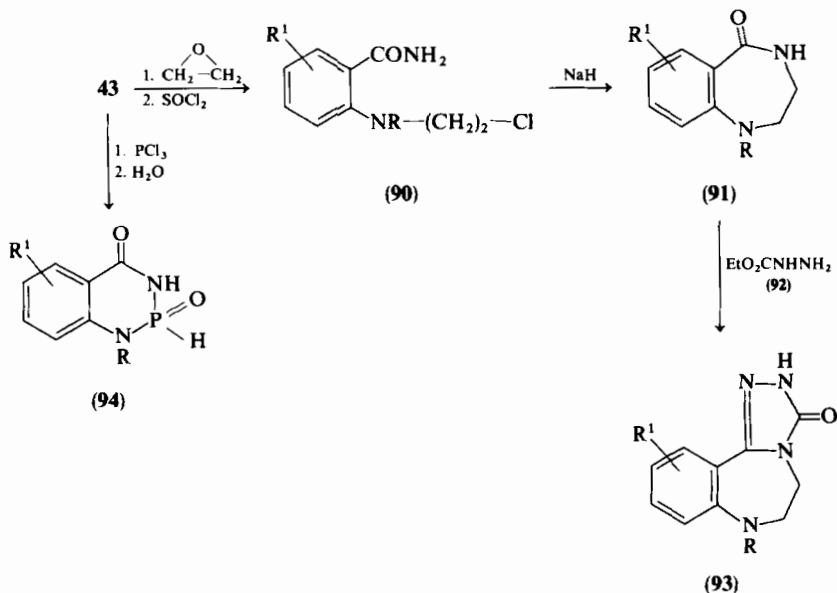
Heteroanalog carbonyl compounds such as thionyl chloride react with **43** to give benzothiadiazines (**89**)^{19,161}; the action of nitrous acid on **43** yields benzotriazinones (**30**)^{57-62,87} (Eq. 12).



4. Miscellaneous Reactions with Anthranilamides

Reaction of **43** with ethylene oxide followed by chlorination with thionyl chloride gives the chloroethyl-substituted amide **90**, which cyclizes with sodium hydride to the benzodiazepine **91**, converted by ethyl carbazate (**92**) to triazolobenzodiazepinones (**93**).¹⁶² When N-substituted anthranilamides are reacted with phosphorus trichloride followed by hydration, benzodiazaphosphorines (**94**)¹⁶³ are obtained (Scheme 16).

Aminoalcohols **95** and **IA** lead to the anthranilamides **96**, which are cyclized by aryl sulfochlorides in refluxing ethanol to form the benzodi-

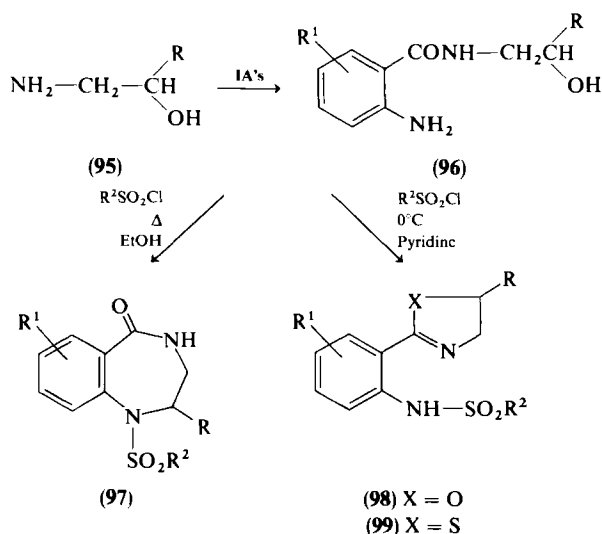


SCHEME 16

¹⁶¹ A. A. Santilli and T. S. Osdene, *J. Org. Chem.* **29**, 2717 (1964).

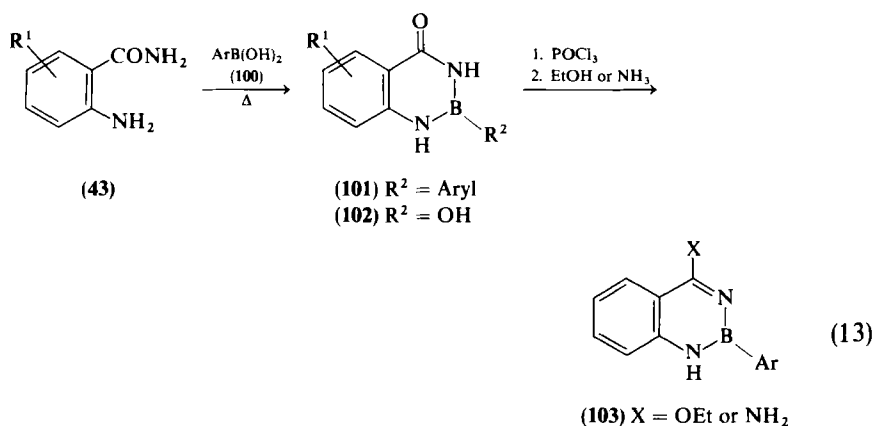
¹⁶² Upjohn Co. (J. B. Hester), U.S. Patent 3,717, 654 (1973) [*CA* **78**, 136352 (1973)].

¹⁶³ G. M. Coppola and R. I. Mansukhani, *J. Heterocycl. Chem.* **15**, 1169 (1978); **16**, 897 (1979).



SCHEME 17

azepinones **97**.¹⁶⁰ Reaction in pyridine at 0°C yields oxazolines (**98**), which with P_2S_5 give the corresponding thiazolines **99**¹⁶⁴ (Scheme 17). Anthranilamides (**43**) with areneboronic acids (**100**) in nonprotic solvents yield benzodiazaborins **101** ($\text{R} = \text{aryl}$) and **102** ($\text{R} = \text{OH}$)¹⁶⁵; the ratio of **101** to **102** depends on the success in removing the water formed during the reaction. In contrast to their carbon isosteres, the boron heterocycles dissolve in aqueous alkali to form stable anions. The adducts of **101** and phosphorus oxychloride give ethoxy- and aminobenzodiaza-borins (Eq. 13).



¹⁶⁴ American Home Products Corp. (by A. A. Santilli and T. S. Osdene), U.S. Patent 3, 452, 032 (1969)[*CA* 71, 81338 (1969)]; G. M. Coppola and G. E. Hardtmann, *Synthesis* 63 (1980).

¹⁶⁵ H. Yale, *J. Heterocycl. Chem.* 8, 193 (1971).

The section concerning reactions of anthranilic acid amides deals solely with published reactions starting from IA.

B. REACTIONS OF HYDRAZIDES AND HYDROXYLAMIDES

Anthranilic acid hydrazides (**104**), prepared from IA and hydrazines,^{10,87,92,166} are used as precursors for quinazolines, benzotriazinones, and benzotriazepines. Cyclization of **104** with formic acid gives 3-aminoquinazolone (**105**)^{167,168}; 3-aminoquinazolinedione (**106**) is obtained from urea and the unsubstituted hydrazide **104** ($R^2 = R^3 = H$),⁷⁶ while ring closure with phosgene or ethyl chloroformate is reported to form triazepine-diones (**107**).^{76,169-171} *N,N'*-Dimethylhydrazide (**104**) ($R^2 = R^3 = Me$) and aldehydes produce the corresponding benzotriazepine **108**.¹⁷¹ Monomethyl-substituted hydrazides **104** ($R^3 = H$) lead, with ortho esters of carboxylic acids, to the triazepines **109**,^{169,172,173} which suffer ring contraction in refluxing sodium ethylate to yield the *N*-methylaminoquinazolones **110**¹⁷² (Scheme 18). Anthranilic acid hydrazides (**104**) with dimethyl acetylenedicarboxylate yield the enamines **111**, which cyclize on heating to quinazolines (**112**) and not triazepines.¹⁷⁴ Cyclization of **104** with nitrous acid yields 3-aminobenzotriazinones (**113**)^{167,175} (Scheme 19).

Spiroquinazolines (**114**) can be obtained from hydrazides **104** and cyclohexanone ($X = CH_2$) or 1-methyl-4-piperidone ($X = NMe$).¹⁷⁶ γ -Ketocarboxylic acids as 2-acetylpropionic acid (**115**) form the condensed quinazolones **116** or **117**, depending on the substitution of the ring and hydrazine nitrogens. With 2-acetylbenzoic acid (**118**), the analogous tetracyclic derivative **119** is obtained^{176,177} (Scheme 20). Half a mole of hydrazine hydrate with one mole

¹⁶⁶ M. S. Gibson and M. Green, *Tetrahedron* **21**, 2191 (1965).

¹⁶⁷ S. Petersen, H. Herlinger, E. Tietze, and W. Siefken, *Angew. Chem.* **74**, 855 (1962).

¹⁶⁸ H. J. Hess, T. H. Cronin, and A. Scriabine, *J. Med. Chem.* **11**, 130 (1968).

¹⁶⁹ S. Sunder, N. P. Peet, and D. L. Trepanier, *J. Org. Chem.* **41**, 2732 (1976).

¹⁷⁰ O. Hromatka, F. Krenmüller, and M. Knollmüller, *Monatsh. Chem.* **100**, 934 (1969).

¹⁷¹ O. Hromatka, F. Krenmüller, and M. Knollmüller, *Monatsh. Chem.* **100**, 941 (1969).

¹⁷² R. W. Leiby and N. D. Heindel, *J. Org. Chem.* **41**, 2736 (1976); **42**, 161 (1977).

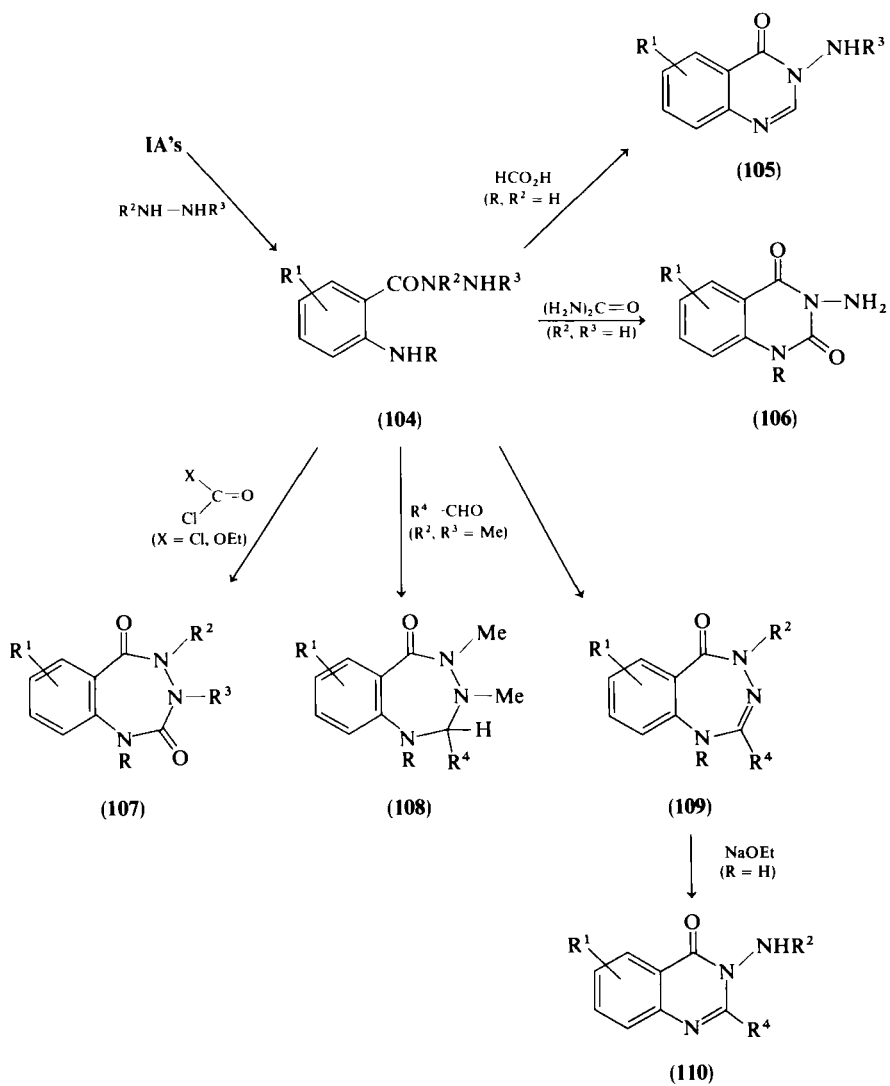
¹⁷³ N. P. Peet and S. Sunder, *J. Heterocycl. Chem.* **13**, 967 (1976).

¹⁷⁴ C. F. Beam, C. A. Park, N. D. Heindel, and W. P. Fives, *J. Heterocycl. Chem.* **14**, 703 (1977).

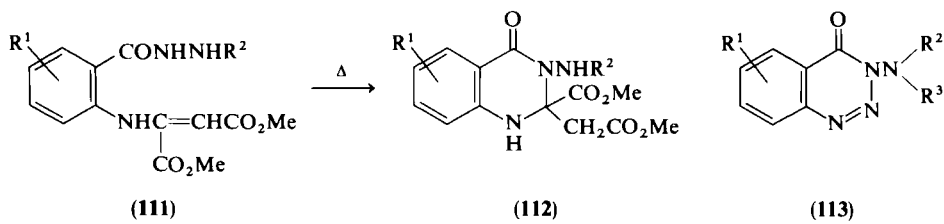
¹⁷⁵ Sandoz-Wander Inc. (by F. G. Kathawala), U.S. Patent 3,818,001 (1974) [*CA* **81**, 105597 (1974)].

¹⁷⁶ Sterling Drug Inc. (by F. K. Kirchner and A. W. Zalay), U.S. Patent 3,843,645 (1974) [*CA* **82**, 112089 (1975)].

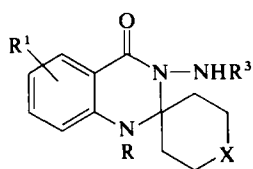
¹⁷⁷ American Hoechst Corp. (by E. H. Wolf and B. J. Duffy), U.S. Patent 3,883,524 (1975) [*CA* **83**, 131624 (1975)].



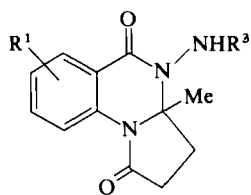
SCHEME 18



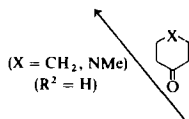
SCHEME 19



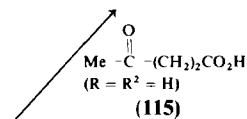
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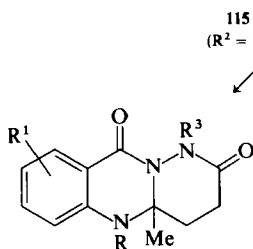
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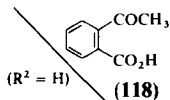
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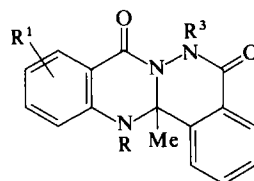
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(117)

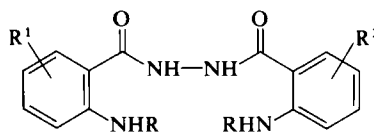


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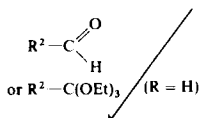
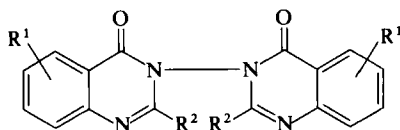


(119)

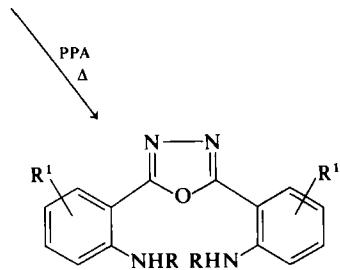
SCHEME 20



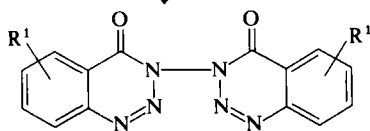
(120)


$$/(\mathbf{R} = \mathbf{H})$$


(121)



(123)

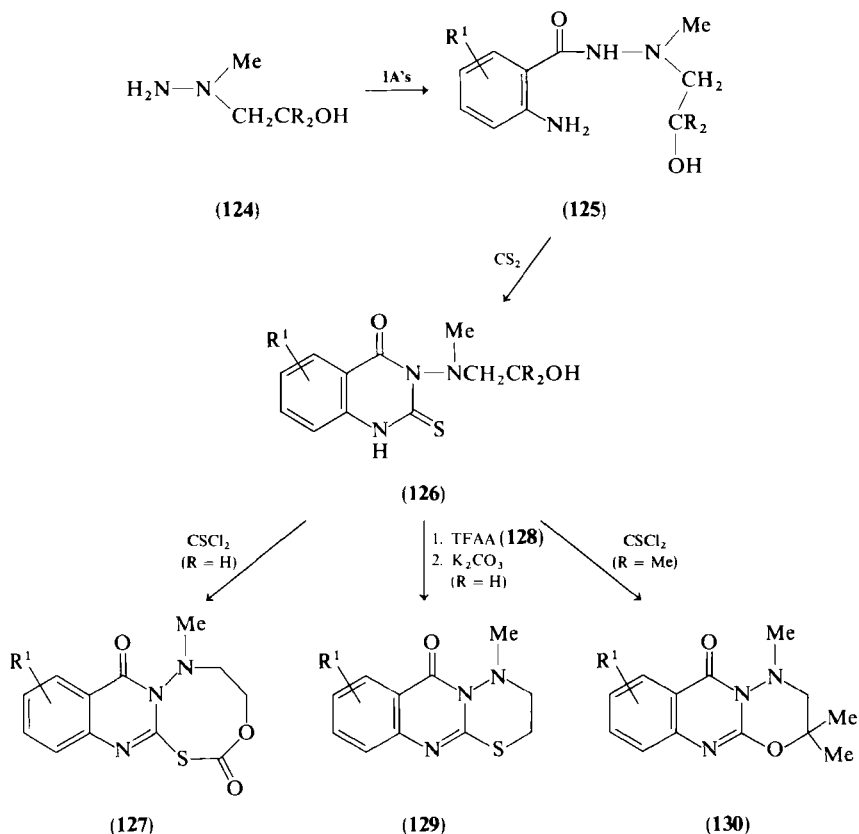


(122)

SCHEME 21

of IA gives the bis-acylhydrazine **120**, which cyclizes normally with carboxylic acids or aldehydes to bis-quinolones (**121**)^{178,179} and with nitrous acid to bis-triazinones (**122**).¹⁷⁸ Heating **120** with polyphosphoric acid forms oxadiazoles (**123**)¹⁷⁹ (Scheme 21).

IA and hydrazinoalcohols (**124**) form the anthranilic acid hydrazides **125**; subsequent reaction with CS₂ gives the thioxoquinazolines **126**, which cyclize with thiophosgene affording oxathiadiazocinoquinazolones (**127**) or oxadiazinoquinazolones (**130**), depending on the substituents. Another cyclization is effected with trifluoroacetic anhydride (**128**) followed by potassium carbonate, yielding thiadiazinoquinazolones (**129**)¹⁸⁰ (Scheme 22).



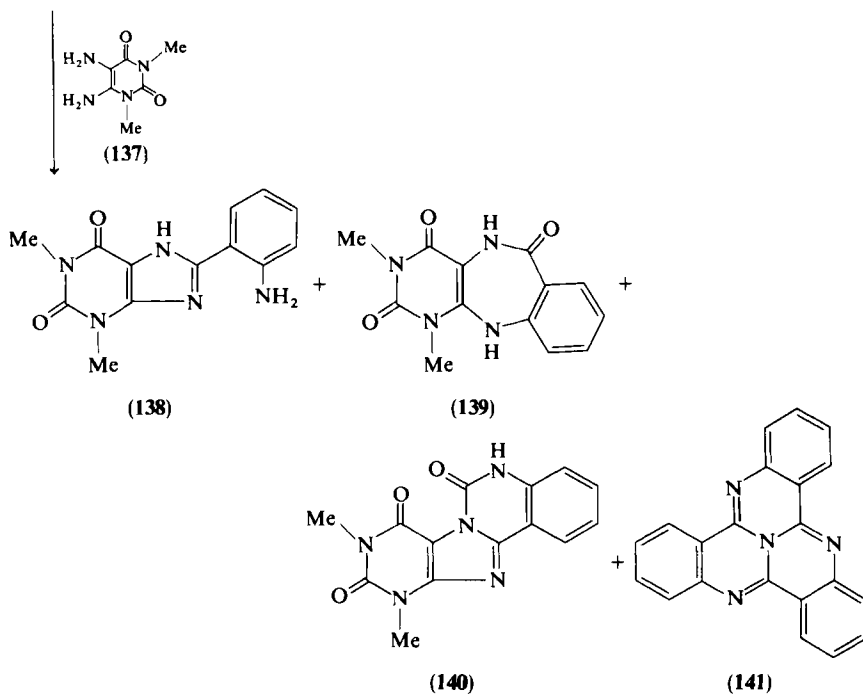
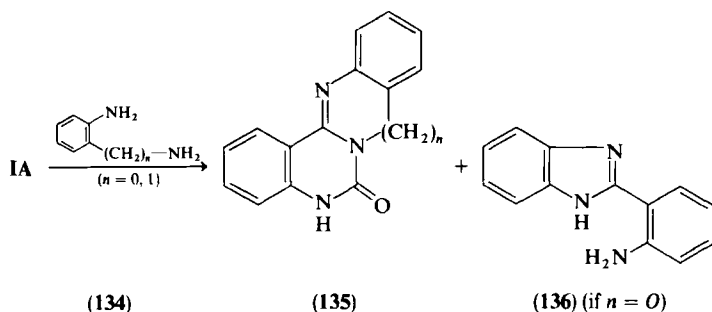
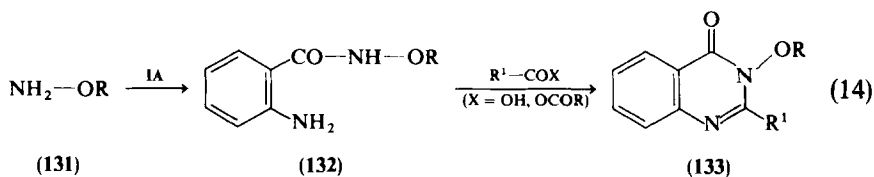
SCHEME 22

¹⁷⁸ Farbwerke Hoechst A. G. (by H. Kohl, N. J. De Souza, J. Patel, and P. D. Desai), Ger. Offen. 2,232,532 (1974) [*CA* **80**, 121007 (1974)].

¹⁷⁹ K. Nagahara and A. Takada, *Chem. Pharm. Bull.* **25**, 2713 (1977).

¹⁸⁰ S. Sunder and N. P. Peet, *Proc. Int. Congr. Heterocycl. Chem.*, 7th, 1979 Abstract, p. 206 (1979); *J. Heterocycl. Chem.* **16**, 1339 (1979).

IA and O-substituted hydroxylamines (131) give anthranilic acid hydroxylamides (132)⁹⁶ (hydroxylamine itself forms the O-acyl derivative⁹⁵). Carboxylic acids and anhydrides cyclize 132 to the quinazolones 133⁹⁶ (Eq. 14).

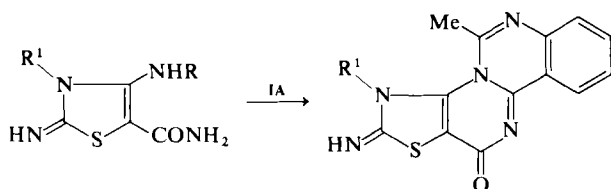


SCHEME 23

C. REACTION OF ISATOIC ANHYDRIDE WITH DIAMINES

Aromatic and araliphatic diamines (**134**) with IA (without isolation of an intermediate anthranilamide) yield the condensed quinazolones **135** in poor yield.¹⁸¹⁻¹⁸³ For *o*-phenylenediamine the main product is the imidazole **136**.¹⁸¹ IA and the uracil **137** furnish a mixture of the theophylline **138** together with the benzodiazepine **139** besides the expected quinazolinone **140** and the tricycloquinazoline **141**.^{181,184} (Scheme 23).

Treatment of the aminothiazoline **142** with IA and cyclization of the expected amide **143** with acetic anhydride forms a condensed quinazoline, either **144** or **145**. Mechanistic considerations favor **144**, but there is no evidence to distinguish them¹⁸⁵ (Eq. 15).

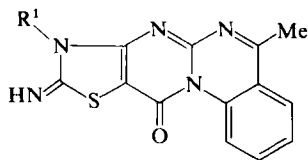


(142) R = H

(143) R = anthraniloyl

(144)

or



(145)

(15)

D. REACTION OF ISATOIC ANHYDRIDE WITH ENAMINES

Ethyl β -aminocrotonate (**146**; R = OEt) or acetylacetone imine (**146**; R = Me) react with IA, with loss of ethyl acetate or acetone,¹⁸⁶ to give the same quinazolone (**87**), also obtained from anthranilamide and acetylacetone (see

¹⁸¹ E. C. Taylor and F. Yoneda, *Angew. Chem.* **79**, 901 (1967); *Angew. Chem., Int. Ed. Engl.* **6**, 878 (1967).

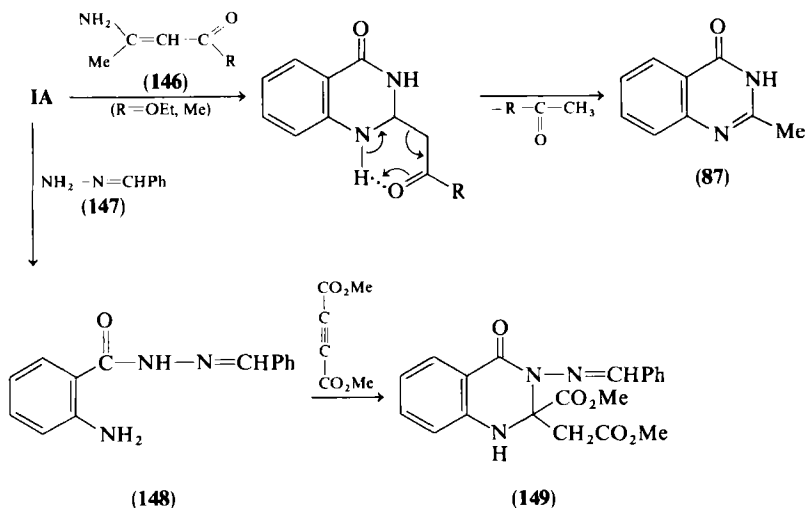
¹⁸² V. P. Arya, K. G. Dave, V. G. Khadse, and S. J. Shenoy, *Indian J. Chem., Sect. B* **14**, 879 (1976).

¹⁸³ A. L. L. Poot, J. F. Willems, and F. C. Hevgebaert, *Bull. Soc. Chim. Belg.* **72**, 365 (1963).

¹⁸⁴ F. Yoneda and K. Mera, *Chem. Pharm. Bull.* **20**, 1815 (1972).

¹⁸⁵ A. Singh, *Res. J. Sci.* **1**, 45 (1974).

¹⁸⁶ C. Mayer and T. Kappe, *Z. Naturforsch., Teil B* **32**, 1214 (1977).



Scheme 15).¹⁶⁰ Similarly, the hydrazone **147** reacts at the amino (and not azomethine) moiety, to yield the amide **148**, which cyclizes with dimethyl acetylenedicarboxylate to give the quinazolinone **149**¹⁷⁴ (Scheme 24).

III. Reaction of Isatoic Anhydride with Carboxylic Acid Derivatives

A. AMIDES

IA with aliphatic and aromatic carboxylic amides (**150**; X = O) gives the quinazolones **151**¹⁸⁷⁻¹⁹¹ (Eq. 16). Lactams similarly yield C-2-N-3 bridged quinazolones^{182,192-196} [e.g., the natural products courupitine A **152**¹⁹⁶ and

¹⁸⁷ J. F. Meyer and E. C. Wagner, *J. Org. Chem.* **8**, 239 (1943).

¹⁸⁸ R. Pater, *J. Heterocycl. Chem.* **8**, 699 (1971).

¹⁸⁹ American Cyanamid Co. (by H. G. Brooks), Ger. Offen. 2,027,791 (1970) [*CA* **74**, 53833 (1971)].

¹⁹⁰ E. Ziegler, W. Steiger, and T. Kappe, *Monatsh. Chem.* **100**, 150, 948 (1969).

¹⁹¹ Sumitomo Chemical Co., Ltd (by E. Yamada, K. Sato, M. Sugihara, and K. Ohtake), Japanese Patent 7,404,810 (1974) [*CA* **81**, 171355 (1974)].

¹⁹² E. Späth and F. Kuffner, *Ber. Dtsch. Chem. Ges.* **71**, 1657 (1938).

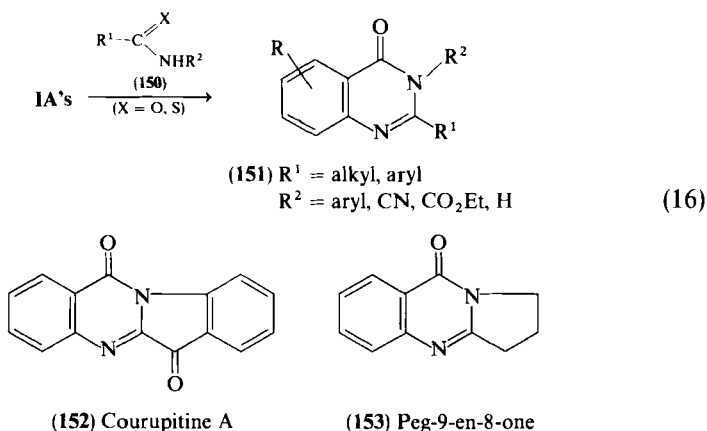
¹⁹³ E. Späth and N. Platzter, *Ber. Dtsch. Chem. Ges.* **68**, 2221 (1935).

¹⁹⁴ K. H. Mentzel, R. Pütter, and G. Wolfrum, *Angew. Chem.* **74**, 839 (1962).

¹⁹⁵ D. B. Reisner, B. J. Ludwig, E. Simon, T. Dejneka, and R. D. Sofia, *Arzneim.-Forsch.* **27**, 766 (1977); Carter Wallace Inc. (by D. B. Reisner, B. J. Ludwig, and F. M. Berger), Ger. Offen. 2, 149, 677 (1972) [*CA* **77**, 34562 (1972)].

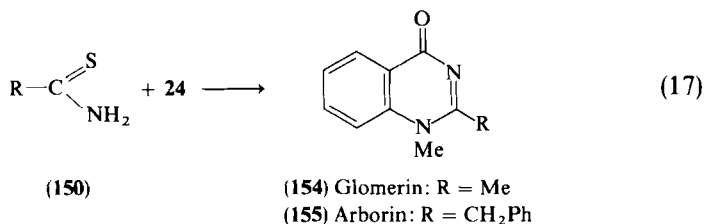
¹⁹⁶ J. Bergman, B. Egstad, and J. O. Lindström, *Tetrahedron Lett.*, 2625 (1977).

peg-9-en-8-one (Späth's numbering) **153**¹⁹³. Similar results were obtained with "sulfinamide anhydride" **32** (Eq. 3).⁶⁴⁻⁶⁸



B. THIOAMIDES

Thioamides (**150**; X = S) react with IA in better yield to the quinazolones **151**¹⁹⁰ [the alkaloid glycosminine (**151**; R¹ = CH₂Ph, R² = H) was obtained in this way) (Eq. 16)]. *N*-Methyl IA (**24**) (cf. Eq. 1) and thioacetamide form the alkaloid glomerin (**154**; R = Me)¹⁹⁰; with phenylacetothioamide the alkaloid arborin (**155**; R = CH₂Ph) was obtained¹⁹⁰ (Eq. 17). Recently, the synthesis of these alkaloids was repeated using "sulfinamide anhydride" (**32**)^{64,67} instead of IA.

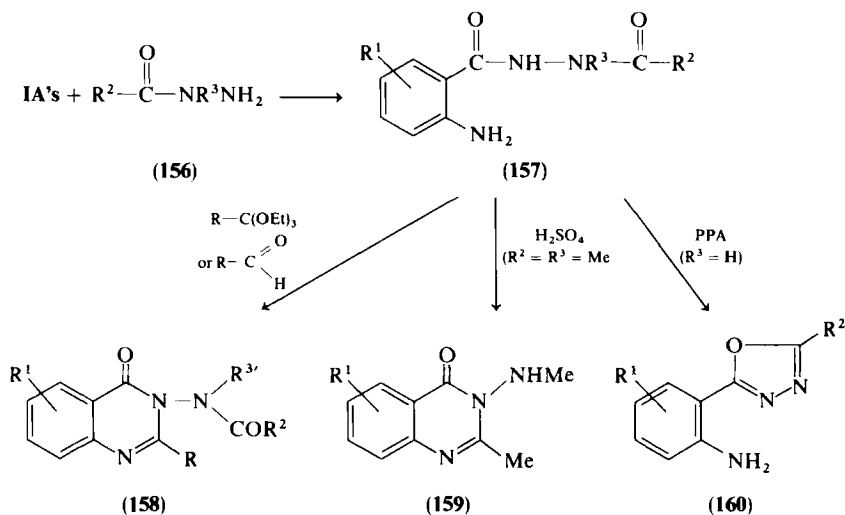


C. HYDRAZIDES

IA with acylhydrazines (**156**) yields **157**, which condenses with ortho esters or aldehydes to the quinazolones **158**.^{197,198} Sulfuric acid cyclizes *N*-acetyl-*N*-methylhydrazine (**156**) to the quinazolinone **159**.¹⁹⁷ Polyphosphoric

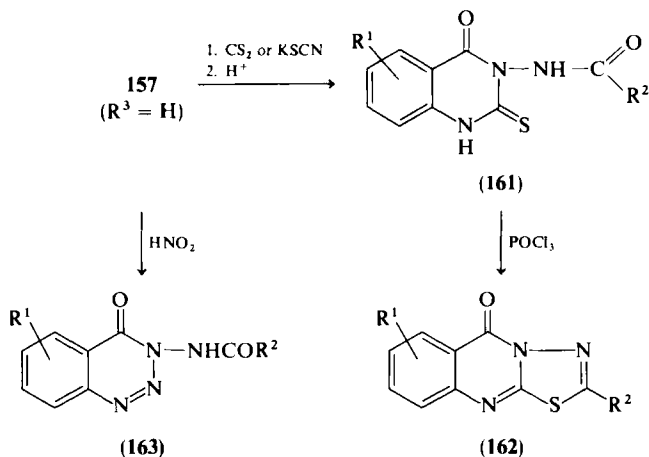
¹⁹⁷ N. P. Peet, S. Sunder, and R. J. Cregge, *J. Org. Chem.* **41**, 2733 (1976).

¹⁹⁸ Farbenfabrik Bayer A. G. (by S. Petersen, E. Tietze, F. Hoffmeister, and W. Wirth), British Patent 932,680 (1964) [*CA* **60**, 4162 (1964)].



SCHEME 25

acid and **157** were reported to yield triazepines¹⁹⁹; however, others have shown that the products are oxadiazoles **160**, confirming the formation of the intermediates **157**^{200–202} (Scheme 25). Ring closure of **157** with CS₂ or



SCHEME 26

¹⁹⁹ American Home Prod. Corp. (by A. L. Langis), U.S. Patent 3,542,767 (1970) [CA 74, 88089 (1970)].

²⁰⁰ M. Takahashi, S. Onizawa, and T. Satoh, *Bull. Chem. Soc. Jpn.* **47**, 2724 (1974).

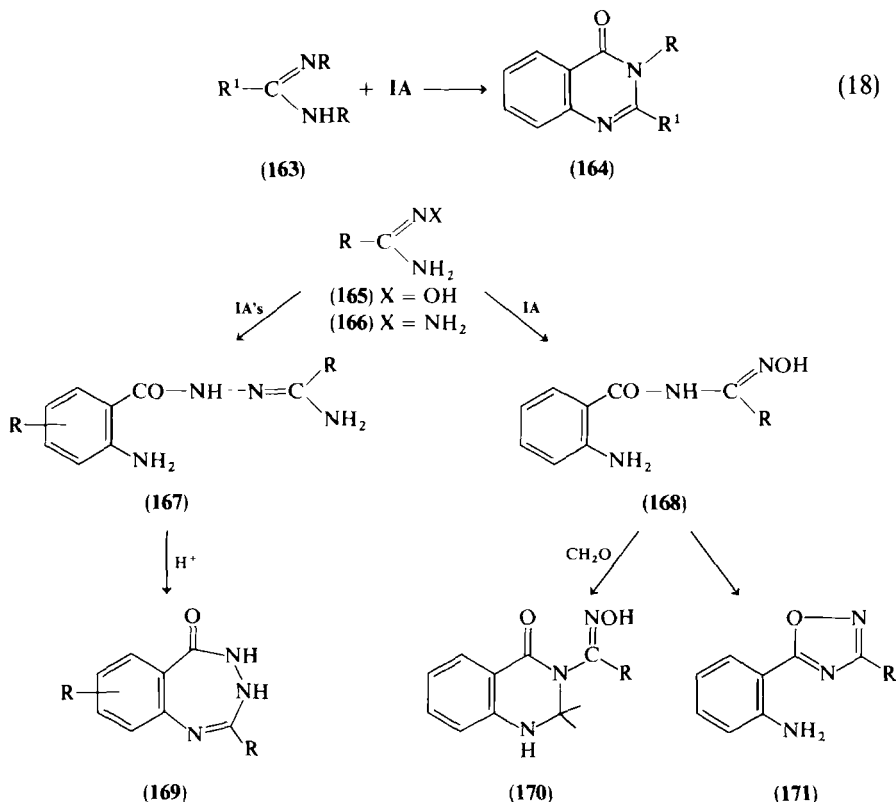
²⁰¹ BASF A. G. (by P. Dimroth and W. Lotsch), Ger. Offen 2,432,838 (1976) [CA 84, 137207 (1976)].

²⁰² BASF A. G. (by P. Dimroth, H. Scheuer, H. Junge, and W. Kurtz), Ger. Offen. 2,417,217 (1975) [CA 84, 61177 (1976)].

KSCN forms the quinazolones **161**, which with POCl_3 give thiadiazoloquinazolinones **162**.²⁰³ Cyclization of **157** with HNO_2 forms benzotriazinones (**163**)^{198,204} (Scheme 26).

D. AMIDINES

IA and amidines (**163**) give quinazolinones **164**^{187,205–207} (Eq. 18). Amidrazones (**166**) with IA give seven-membered triazepines (**169**).²⁰⁰ With amidoximes the intermediate **168** is obtained, which is cyclized by formaldehyde



SCHEME 27

²⁰³ S. K. Modi, V. Kumar, and K. S. Narang, *Indian J. Chem.* **8**, 710 (1970).

²⁰⁴ Hoechst A. G., British Patent 1,429,339 (1976) [*CA* **85**, 63095 (1976)].

²⁰⁵ Hisamitsu Pharmaceutical Co., Inc. (by T. Hisano, M. Ichikawa, H. Ide, K. Noda, A. Nakagawa, and T. Motomura), Japanese Kokai 73/62, 772 (1973) [*CA* **79**, 146542 (1973)].

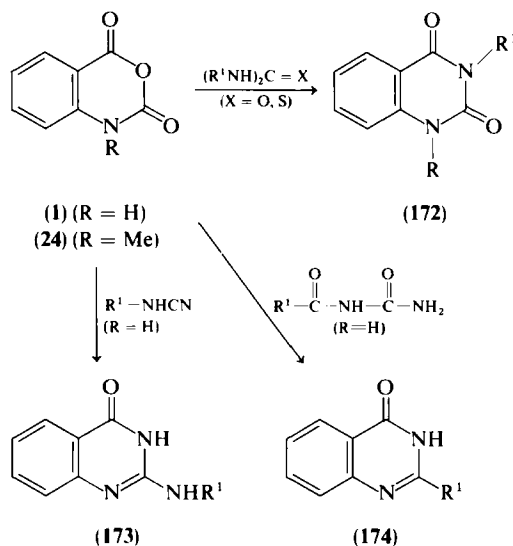
²⁰⁶ K. Nagahara, K. Takagi, and T. Ueda, *Chem. Pharm. Bull.* **24**, 1197 (1976).

²⁰⁷ M. Takahashi, S. Onizawa, and R. Shioda, *Nippon Kagaku Kaishi* **8**, 1259 (1972) [*CA* **78**, 72078 (1973)].

to the quinazolinone **170**.²⁰⁷ Treatment of **168** with acid or base catalyst gives oxadiazoles (**171**)²⁰⁸⁻²¹⁰ (Scheme 27).

E. UREAS, THIOUREAS, AND CYANAMIDES

Ureas and thioureas react with IA (**1** and **24**) to form quinazolinediones (**172**).^{97,211} In this way the alkaloid glycosmicin (**172**; $R^1 = H$, $R = Me$)^{190,211} was synthesized. Cyanamides and IA yield the 2-aminoquinazolinones **173**²¹²; with acylureas the quinazolinones **174** were produced²¹³⁻²¹⁶ (Scheme



SCHEME 28

²⁰⁸ BASF A. G. (by H. Junge, W. Kurtz, P. Dimroth, and H. Scheuer). Ger. Offen. 2,457,687 (1976) [*CA* **85**, 95739 (1976)]; BASF A. G. (by W. Kurtz, D. Horn, and W. Diller), Ger. Offen. 2,721,955 (1978) [*CA* **90**, 105613 (1979)].

²⁰⁹ K. Nagahara, K. Takagi, and T. Ueda, *Chem. Pharm. Bull.* **23**, 3178 (1975).

²¹⁰ H. L. Yale and E. R. Spitzmiller, *J. Heterocycl. Chem.* **15**, 1373 (1978).

²¹¹ W. Steiger, T. Kappe, and E. Ziegler, *Monatsh. Chem.* **100**, 528 (1969).

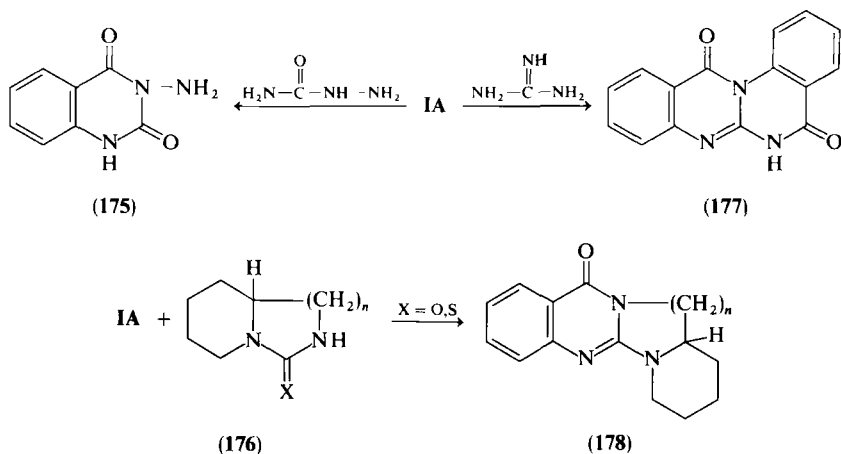
²¹² E. Ziegler, W. Steiger, and T. Kappe, *Monatsh. Chem.* **99**, 1499 (1968).

²¹³ Sumitomo Chemical Co., Ltd (by E. Shigaru, K. Satoh, and G. Suzuki), Japanese Patent 7,332,409 (1973) [*CA* **81**, 65222 (1974)].

²¹⁴ Sandoz Patent GmbH (by W. Koch), Ger. Offen. 2,447,878 (1975) [*CA* **83**, 116962 (1975)].

²¹⁵ Sandoz Ltd. (by W. Koch), Ger. Offen. 2,306,843 (1973) [*CA* **80**, 49260 (1974)].

²¹⁶ Sandoz Wander Inc. (by W. Koch), U.S. Patent 4,007,188 (1977) [*CA* **86**, 173073 (1977)].



SCHEME 29

28). Semicarbazide gives 3-aminoquinazolin-2(1H)-one (**175**).^{76,207} Reaction of IA with guanidine forms the diquinazolinone **177**²⁰⁷ and with cyclic ureas such as **176** tetracyclic quinazolones (**178**) are produced²¹⁷ (Scheme 29).

F. ISOTHIUREAS

Isothioureas (**179**) heated with IA in aqueous media give quinazolin-2(1H)-ones (**180**).²¹² Heating in dry solvents (e.g. DMF) leads to quinazolinones **181**,^{212,218-222} **182**,^{211,223} or **183**.^{211,212,220} (Scheme 30). Cyclic isothioureas (**184**) yield imidazo ($n = 1$) or pyrimido ($n = 2$) -quinazolones (**185**).²¹²

²¹⁷ G. E. Hardtmann, B. S. Huegi, J. H. Gogerty, L. C. Iorio, and W. H. Barnes, *J. Med. Chem.* **14**, 878 (1971).

²¹⁸ Sandoz Wander Inc. (by G. E. Hardtmann), U.S. Patent 4,020,062 (1977) [*CA* **87**, 35039 (1977)].

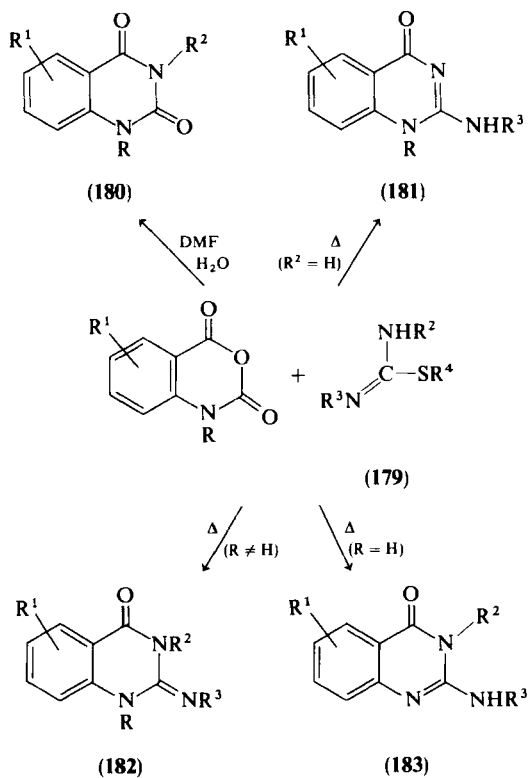
²¹⁹ Sandoz Wander Inc. (by G. E. Hardtmann), U.S. Patent 3,963,453 (1976) [*CA* **84**, 164,832 (1976)].

²²⁰ G. M. Coppola, G. E. Hardtmann, and O. R. Pfister, *J. Org. Chem.* **41**, 825 (1976); G. M. Coppola and G. E. Hardtmann, *J. Heterocycl. Chem.* **16**, 1605 (1979); Sandoz Inc. (by G. E. Hardtmann), U.S. Patent 4,117,137 (1978) [*CA* **90**, 54834 (1979)].

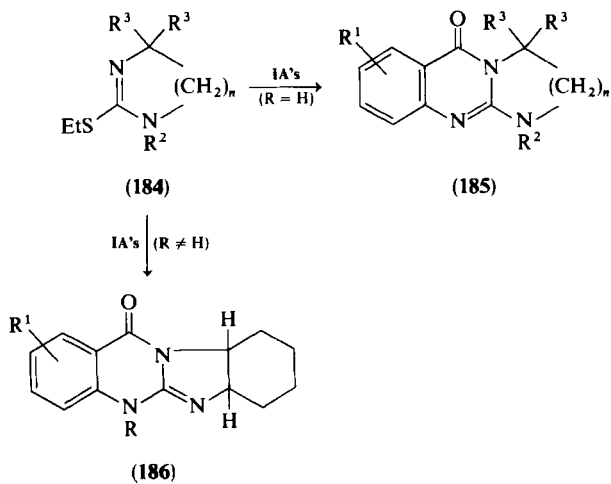
²²¹ G. E. Hardtmann, G. Koletar, O. R. Pfister, J. H. Gogerty, and L. C. Iorio, *J. Med. Chem.* **18**, 447 (1975).

²²² G. M. Coppola, *J. Heterocycl. Chem.* **15**, 645 (1978).

²²³ Sandoz Wander Inc. (by G. E. Hardtmann), U.S. Patent 3,959,279 (1976) [*CA* **85**, 78159 (1976)].



SCHEME 30



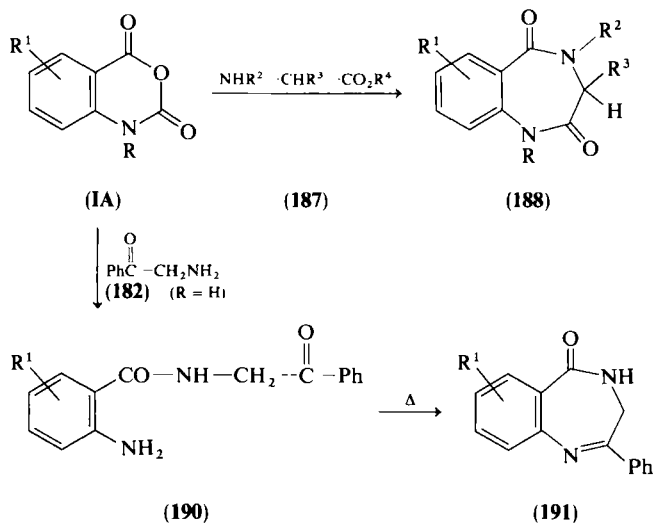
SCHEME 31

Recently, this reaction was used to prepare a number of pharmaceutically active tri- and tetracyclic quinazolinones (e.g., **186**²²¹)^{212,217,218,220,224-239} (Scheme 31).

G. α -AMINO ACIDS AND α -AMINOKETONES

α -Amino acids (**187**) (glycine,^{240,241} glycine ethyl ester,^{207,242-244} and N-substituted glycine esters^{242,245}) undergo ring closures with IA resulting

- ²²⁴ Sandoz Wander Inc. (By G. E. Hardtmann), U.S. Patent 3,969,506 (1976) [*CA* **86**, 5485 (1977)].
- ²²⁵ Sandoz Wander Inc. (By G. E. Hardtmann), U.S. Patent 3,978,059 (1976) [*CA* **86**, 29867 (1977)].
- ²²⁶ Sandoz Wander Inc. (by G. E. Hardtmann), U.S. Patent 4,013,646 (1977) [*CA* **87**, 23325 (1977)]; U.S. Patent 3,975,386 (1976) [*CA* **86**, 5487 (1977)]; U.S. Patent 3,868, 372 (1975) [*CA* **83**, 28269 (1975)].
- ²²⁷ T. Jen, B. Dienel, H. Bowman, J. Petta, A. Heet, and B. Loev, *J. Med. Chem.* **15**, 727 (1972).
- ²²⁸ Sandoz Wander Inc. (by G. E. Hardtmann), U.S. Patent 4,025,511 (1977) [*CA* **87**, 85044 (1977)].
- ²²⁹ Sandoz Wander Inc. (by G. E. Hardtmann), U.S. Patent 3,963,720 (1976) [*CA* **85**, 160146 (1976)].
- ²³⁰ Sandoz Ltd. (by G. E. Hardtmann), Ger. Offen. 2,257,376 (1973) [*CA* **79**, 42540 (1973)].
- ²³¹ Smith Kline and French Lab. (by T. Y. Jen and B. Loev), U.S. Patent 3,745,216 (1973) [*CA* **79**, 92273 (1973)]; Smith Kline Corp. (by D. W. Blackburn, R. F. Devenney, and T. Y. Jen), U.S. Patent 3,790,573 (1974) [*CA* **80**, 83038 (1974)].
- ²³² Sandoz Ltd. (by G. E. Hardtmann), Ger. Offen. 2,319,851 (1973) [*CA* **80**, 27284 (1974)].
- ²³³ Sandoz Wander Inc. (by G. E. Hardtmann), U.S. Patent 3,772,230 (1973) [*CA* **80**, 59956 (1974)].
- ²³⁴ Sandoz Ltd. (by G. E. Hardtmann), Ger. Offen. 2,402,454 (1974) [*CA* **81**, 120678 (1974)].
- ²³⁵ Sandoz Wander Inc. (by G. E. Hardtmann), U.S. Patent 3,919,210 (1975) [*CA* **84**, 59548 (1976)].
- ²³⁶ Sandoz Wander Inc. (by G. E. Hardtmann), U.S. Patent 3,912,731 (1975) [*CA* **84**, 74299 (1976)].
- ²³⁷ Sandoz Ltd. (by G. E. Hardtmann), U.S. Patent 3,894,022 (1975) [*CA* **83**, 164225 (1975)].
- ²³⁸ G. E. Hardtmann, U.S. Patents 3,875,160, 3,875,161 (1975) [*CA* **83**, 79274 (1975)].
- ²³⁹ Sandoz Ltd. (by G. E. Hardtmann), South African Patent 7,302,111 (1974) [*CA* **83**, 97352 (1975)].
- ²⁴⁰ A. Ermili and G. Filacchioni, *Ann. Chim. (Rome)* **59**, 770 (1969).
- ²⁴¹ American Home Products Corp. (by D. H. Kim), U.S. Patent 3,925,361 (1975) [*CA* **84**, 105665 (1976)].
- ²⁴² D. H. Kim, *J. Heterocycl. Chem.* **12**, 1323 (1975).
- ²⁴³ American Home Products Corp. (by D. H. Kim), U.S. Patent 3,904,603 (1975) [*CA* **83**, 193413 (1975)].
- ²⁴⁴ J. H. Gogerty, R. G. Griot, D. Habeck, L. C. Iorio, and W. J. Houlian, *J. Med. Chem.* **20**, 952 (1977).
- ²⁴⁵ P. M. Carabateas and L. S. Harris, *J. Med. Chem.* **9**, 6 (1966).



SCHEME 32

in benzodiazepines (**188**). Cyclic α -amino acids (proline,^{246–252} hydroxyproline,^{249,253} and related N- and S-ring systems^{249,254,255}) give the corresponding tricyclic benzodiazepines [**188**; R²—R³ = (CH₂)₃, CH(OH)CH₂CH₂, CH₂SCH₂, and many others]. ω -Aminoacetophenone (**189**) and IA react to form **190**, which cyclizes on heating to benzodiazepine **191**^{256,257} (Scheme 32).

²⁴⁶ Sterling Drug Inc. (by P. M. Carabateas), U.S. Patent 3,860,600 (1975) [CA **83**, 58892 (1975)].

²⁴⁷ American Cyanamid Co. (by W. B. Wright), Ger. Offen. 2,513,417 (1975) [CA **84**, 59602 (1976)].

²⁴⁸ American Cyanamid Co. (By W. B. Wright), U.S. Patent 3,947,408 (1976) [CA **85**, 46771 (1976)].

²⁴⁹ Sterling Drug Inc. (by P. M. Carabateas), U.S. Patent 3,732,212 (1973) [CA **79**, 42570 (1973)].

²⁵⁰ American Cyanamid Co. (by W. B. Wright), U.S. Patent 3,968,230 (1976) [CA **85**, 112758 (1976)].

²⁵¹ American Cyanamid Co. (By W. B. Wright), U.S. Patent 3,984,562 (1976) [CA **86**, 55500 (1977)].

²⁵² W. B. Wright, U.S. Patent 3,985,732 (1977) [CA **86**, 29897 (1977)].

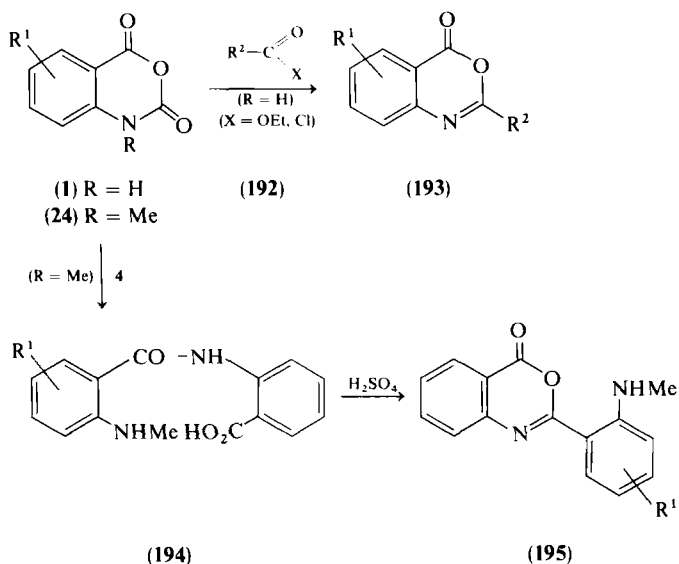
²⁵³ Fujisawa Pharmaceutical Co., Ltd. (by K. Karigome and H. Yazawa), Japanese Patent 74/25,277 (1974) [CA **82**, 140192 (1975)].

²⁵⁴ W. B. Wright, H. J. Brabander, E. N. Greenblatt, I. P. Day, and R. A. Hardy, *J. Med. Chem.* **21**, 1087 (1978).

²⁵⁵ R. B. Stevens, R. M. Corey, and S. Rossens, *J.C.S., Chem. Comm.*, 742 (1975).

²⁵⁶ F. P. Woerner, H. Reimlinger, and R. Merenyi, *Chem. Ber.* **104**, 2789 (1971).

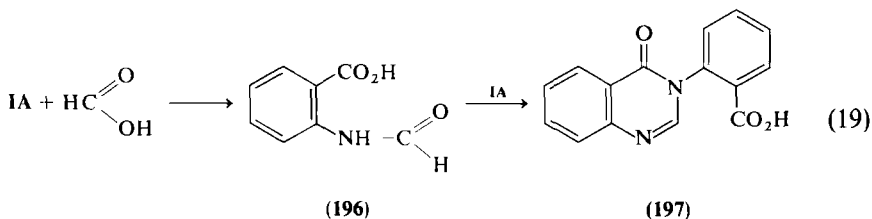
²⁵⁷ A. A. Santilli and T. S. Osdene, *J. Org. Chem.* **29**, 1998 (1964).



SCHEME 33

H. OTHER CARBOXYLIC ACID DERIVATIVES

Alkyl- and aryl-substituted carboxylic acid derivatives such as ethyl 4-methoxybenzoate, diethyl phthalate,¹⁰⁴ aryl- and alkylcarboxylic acid halides or anhydrides^{10,258} give benzoxazinones (193). When IA was brominated in glacial acetic acid, 193 (R² = CHBr₂) was obtained.²⁵⁹ Anthranilic acid (4) with *N*-methyl IA (24) leads to 194, which cyclizes in sulfuric acid to the benzoxazinone 195¹³⁴ (Scheme 33). Reaction of *N*-formylanthranilic acid (196) (available from IA and formic acid) with IA again yields the quinoxalinone 197^{10,260} (Eq. 19).



²⁵⁸ Sherwin Williams Co. (by R. L. Jacobs and R. L. Hively), Ger. Offen. 2,556,590 (1976) [CA 85, 160115 (1976)].

²⁵⁹ R. Bertelson and W. Becker, *J. Heterocycl. Chem.* **3**, 422 (1966).

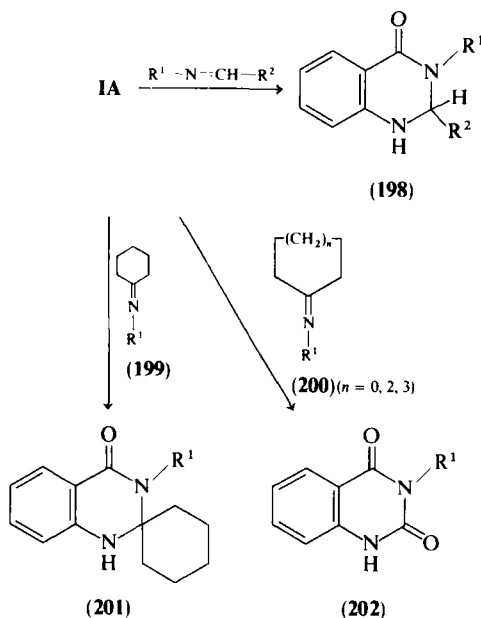
²⁶⁰ R. Anschütz and O. Schmidt, *Ber. Dtsch. Chem. Ges.* **35**, 3470 (1902).

IV. Reactions of Isatoic Anhydride with C=N Double Bonds

Carbon–nitrogen double bond systems such as azomethines or heterocumulenes react with IA with loss of CO₂. For mechanistic considerations see Section I,C.

A. AZOMETHINES

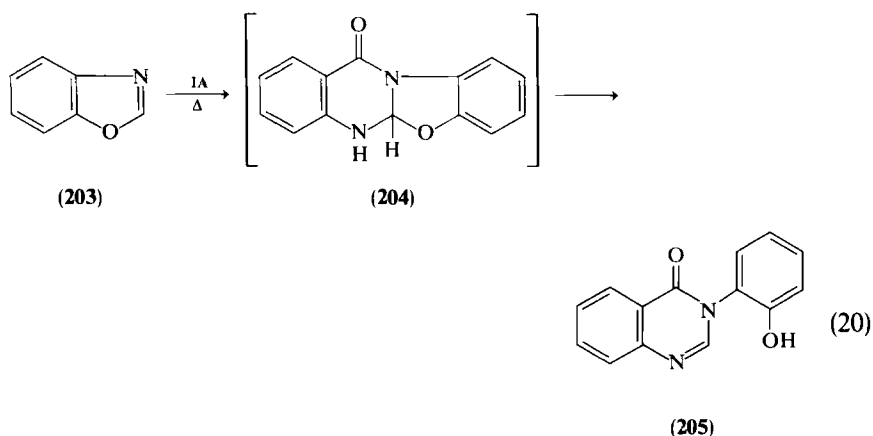
Treatment of IA with azomethines leads to 1,2-dihydroquinazolinones (**198**).^{261,262} With cyclohexanone anil (**199**), a spiro compound (**201**) is obtained; however, five-, seven-, and eight-membered anils (**200**) gave only quinazolinones (**202**)²⁶² (Scheme 34). Benzoxazole (**203**) and IA do not form the expected tetracyclic adduct **204**, but yield the quinazolinone **205**⁹⁸ by ring opening (Eq. 20).



SCHEME 34

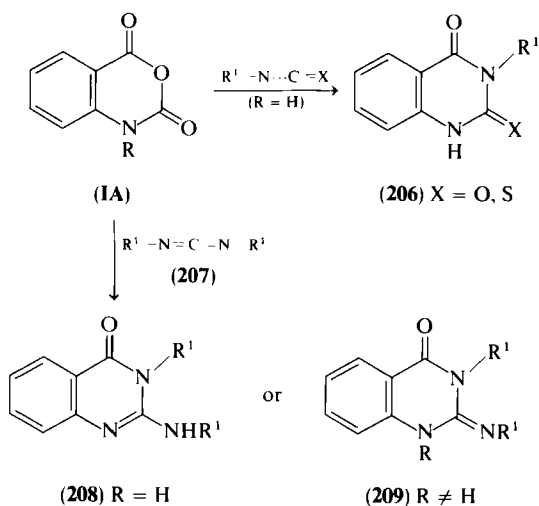
²⁶¹ R. P. Staiger, C. L. Moyer, and G. R. Pitcher, *J. Chem. Eng. Data* **8**, 454 (1963).

²⁶² W. Steiger, T. Kappe, and E. Ziegler, *Monatsh. Chem.* **100**, 146 (1969).



B. HETEROCUMULENES

Aryl isocyanates and isothiocyanates with IA give the quinazolinones **206**.^{261,263} Carbodiimides (207) yield either the aminoquinazolinones **208** (from IA)²¹² or the imino derivatives **209** (from N-substituted IA)²¹¹ (Scheme 35).

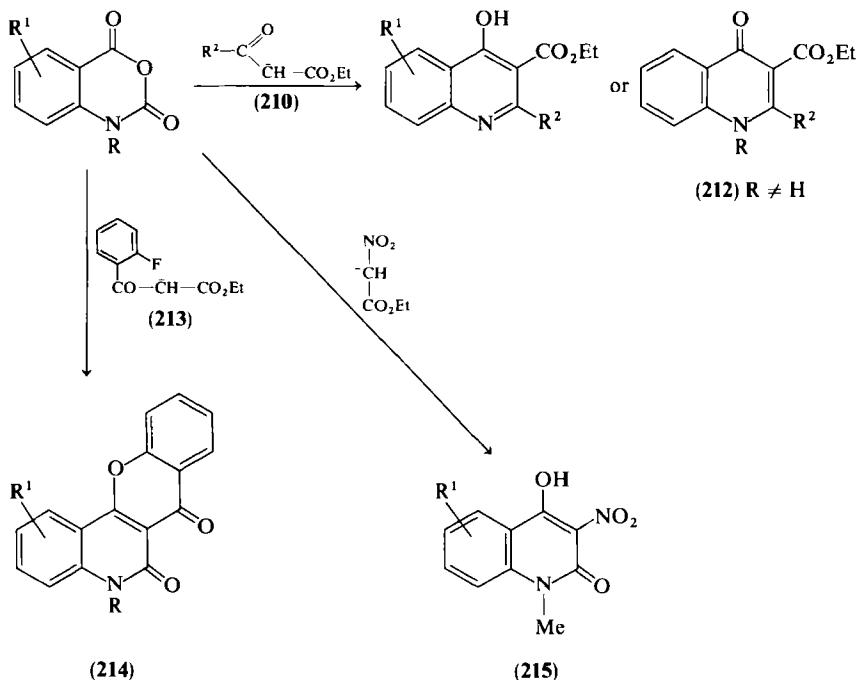


SCHEME 35

²⁶³ K. Srivastava, *Indian J. Appl. Chem.* **34**, 113 (1971); C. Wang, T. C. Feng, and B. E. Christensen, *J. Am. Chem. Soc.* **72**, 4887 (1950).

V. Reactions of Isatoic Anhydride with Carbanions

Compounds containing active methylene groups adjacent to carbonyl react with IA to give quinoline derivatives. Staiger and Miller⁸³ obtained the quinoline **211** ($R^2 = \text{Me}$) by reaction of IA with sodium ethyl acetoacetate (**210**). This reaction was extended to other 1,3-dicarbonyl compounds yielding either the quinolones **212**, for $R = \text{H}$ can tautomerize to **211**.^{220,264,265} Nitroacetate furnishes **215**.^{220,266} *o*-Fluorobenzoyl acetate (**214**) was shown to give a product which ring closes again to form the benzopyranoquinolinedione **214**²⁶⁷ (Scheme 36). Malonic acid esters give carbostyrils (**216**)²²⁰.



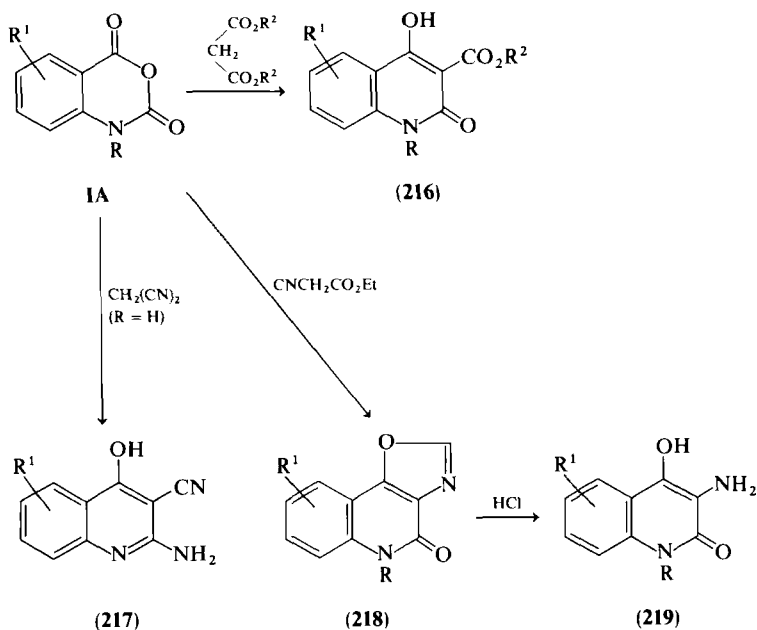
SCHEME 36

²⁶⁴ L. A. Mitscher, H. E. Gracey, G. W. Clark, and T. Suzuki, *J. Med. Chem.* **21**, 485 (1978); L. A. Mitscher, D. L. Flynn, H. E. Gracey, and S. D. Drake, *ibid.* **22**, 1354 (1979).

²⁶⁵ M. R. Bell, A. W. Zalay, R. Oesterlin, P. Shane, and G. O. Potts, *J. Med. Chem.* **13**, 664 (1970); Sterling Drug Inc. (by R. M. Bell), U.S. Publ. Patent Application B 402,162 (1976) [*CA* **85**, 46425 (1976)].

²⁶⁶ Sandoz Patent GmbH (by G. E. Hardtmann), Ger. Offen. 2,631,317 (1977) [*CA* **86**, 189742 (1977)].

²⁶⁷ Sandoz Wander Inc. (G. E. Hardtmann and G. M. Coppola), U.S. Patent 4,017,499 (1977) [*CA* **87**, 39454 (1977)]; G. M. Coppola and G. E. Hardtmann, *J. Heterocycl. Chem.* **16**, 829 (1979).



SCHEME 37

^{264,268-272}; malonodinitrile yields the 2-aminoquinoline **217**.^{207,220,273} Ethyl isocyanoacetate reacts with IA to give oxazoloquinolinones (**218**), which suffer ring cleavage with HCl to give 3-amino-4-hydroxycarbostyryls (**219**).^{19,220,274} (Scheme 37).

Sulfonylmethylene compounds such as methyl sulfonylacetate (**220**; $\text{R}^2 = \text{Me}$, $\text{R}^3 = \text{OEt}$) or phenyl phenacyl sulfone (**220**; $\text{R}^2 = \text{R}^3 = \text{Ph}$) give with N-substituted IA the corresponding 4-hydroxy-3-sulfonyl-2-quinolones

²⁶⁸ D. R. Shridar, C. V. Reddy Sastry, A. K. Mehrotra, C. Seshagiri Rao, and V. Taneja, *Indian J. Chem., Sect. B* **17**, 488 (1979).

²⁶⁹ Sandoz Ltd. (by G. E. Hardtmann), Fr. Demande 2,205,327 (1974) [*CA* **83**, 147400 (1975)]; Ger. Offen. 2,706,752 (1977) [*CA* **88**, 6753 (1978)]; Ger. Offen. 2,354,145 (1974) [*CA* **81**, 37488 (1974)].

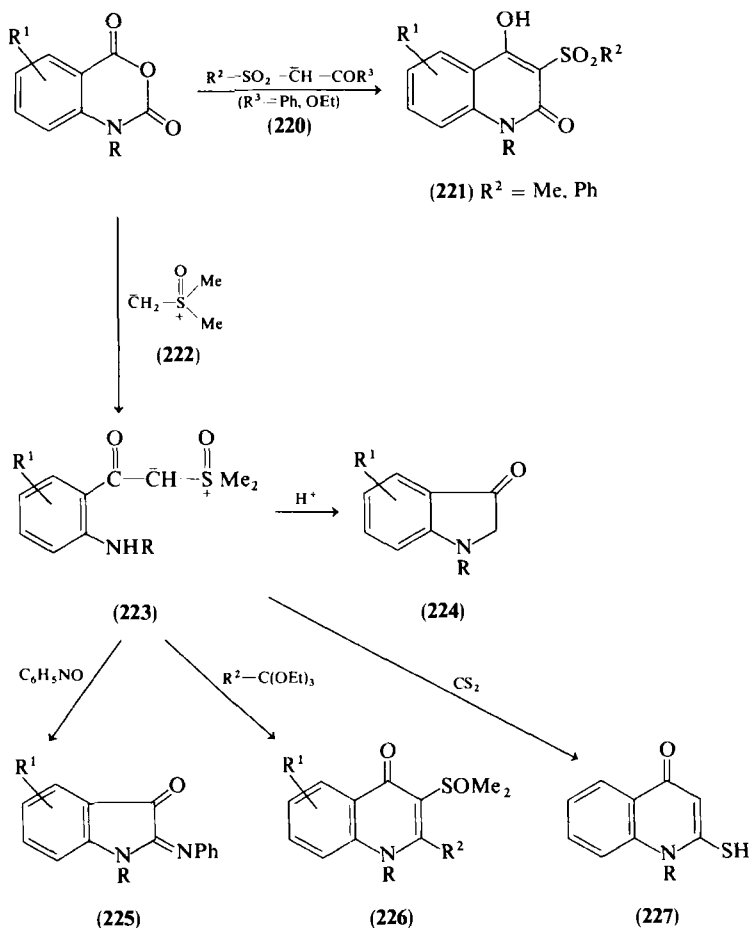
²⁷⁰ Ciba Geigy A. G. (by P. G. Ferrini, G. Haas, and A. Rossi), Swiss Patent 578,536 (1976) [*CA* **86**, 29659 (1977)].

²⁷¹ L. A. Mitscher, G. W. Clark, T. Suzuki, and M. S. Bathala, *Heterocycles* **3**, 913 (1975).

²⁷² Sandoz Inc. (by G. E. Hardtmann), U.S. Patent 4,119,720 (1979) [*CA* **90**, 54843 (1979)].

²⁷³ S. B. Kadin and C. H. Lamphere, *Synthesis*, 500 (1977); Pfizer Inc. (by S. B. Kadin), Ger. Offen. 2,801,248 (1978) [*CA* **89**, 146784 (1978)].

²⁷⁴ M. Suzuki, K. Matsumoto, M. Miyoshi, N. Yoneda, and R. Ishida, *Chem. Pharm. Bull.* **25**, 2602 (1977); Tanabe Seiyaku Co., Ltd. (by M. Miyoshi, N. Yoneda, K. Matsumoto, and M. Suzuki), Japanese Kokai 77/46,085 (1977) [*CA* **87**, 135110 (1977)].



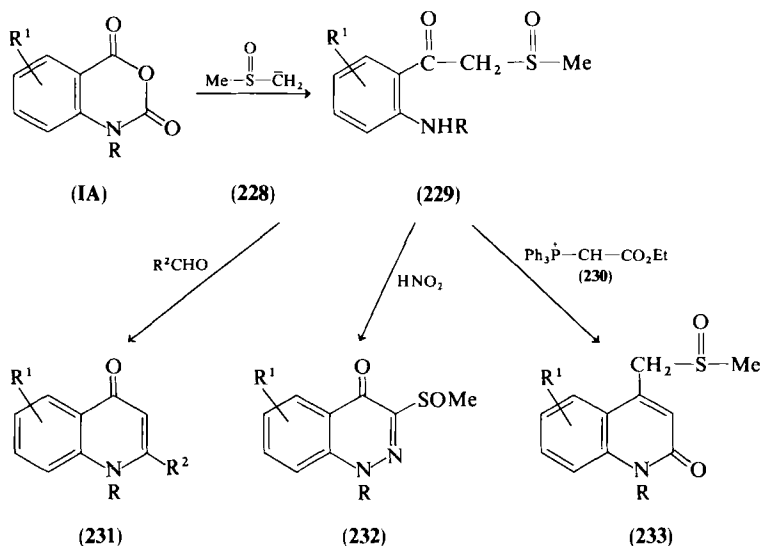
SCHEME 38

221.^{19,220} Reaction of the carbanion **222** results in the formation of the acetophenone ylid **223**, which on treatment with acids or nitrosobenzene is converted to the indole derivatives **224** or **225**.²⁷⁵ Ring closure of **223** with orthoesters yields the quinolones **226**^{275,276}; with carbon disulfide **227** is obtained²⁷⁵ (Scheme 38). Treatment of IA with dimsyl sodium (**228**) leads to **229**, from which with aldehydes the quinolinones **231** are obtained.^{265,277} Reaction with HNO_2 leads to the cinnoline **232**,²⁷⁷ and with carboxy-

²⁷⁵ A. M. van Leusen and E. C. Taylor, *J. Org. Chem.* **33**, 66 (1968).

²⁷⁶ R. Albrecht, *Chim. Ther.* **8**, 45 (1973).

²⁷⁷ M. von Strandmann, S. Klutchko, M. P. Cohen, and J. Shavel, *J. Heterocycl. Chem.* **9**, 173 (1972); Warner Lambert Co. (by M. von Strandmann, J. Shavel, S. Klutchko, and M. Cohen), U.S. Patent 3,798,219 (1974) [*CA* **80**, 146187 (1974)].



SCHEME 39

methylene triphenylphosphorane (230) the quinolinone 233 is formed²⁷⁸ (Scheme 39).

Two novel routes for the preparation of indigo starting with IA have been developed recently.²⁷⁹ As just described (Scheme 39) dimsyl sodium and IA yield 229, which can be converted, via 235 or directly, to indigo (237) in 39% yield. A more satisfactory yield (77%) of the Pummerer rearrangement was observed when 229 ($R = H$) was first acetylated in benzene to 234. Indigo was also obtained by a Nef reaction from 236, which is available from IA and nitromethane anion followed by acetylation²⁷⁹ (Scheme 40). Quinolinonephosphonic esters (239) are isolated from the reaction of IA with cyanomethyl phosphonate (238).^{220,280} With butyrolactone phosphonate (240) and unsubstituted IA ($1; R = H$) the benzoxazine 241 is obtained. Heating 240 and N-substituted IA in a sealed tube with benzene solvent yields the benzoxazine 242, while a DMF solvent forms the furoquinoline 243, also available from 242 by rearrangement in DMF²⁸¹ (Scheme 41). The phosphonium ylid 244 gives with IA a quinoline phosphonium ylid (245).²⁸² With pyridinium ester betaines (246), the formation of the

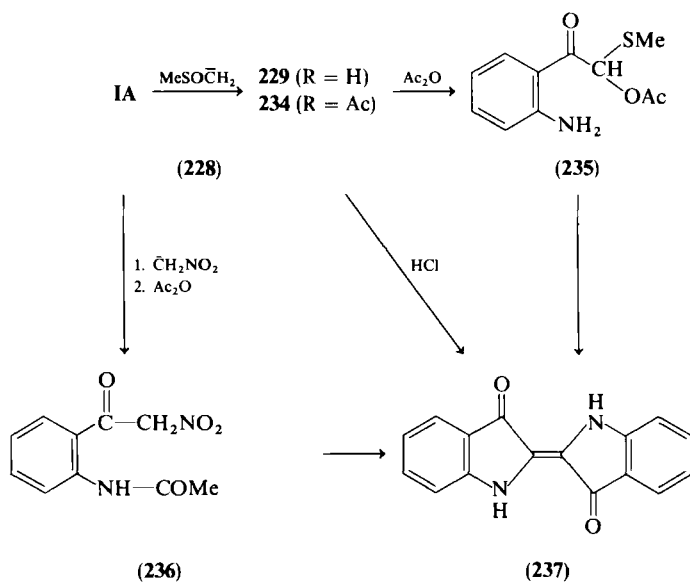
²⁷⁸ M. von Strandman, D. Connor, and J. Shavel, *J. Heterocycl. Chem.* **9**, 1975 (1972).

²⁷⁹ J. Gosteli, *Helv. Chim. Acta* **60**, 1980 (1977); Ger. Offen. 2,658,306 (1978).

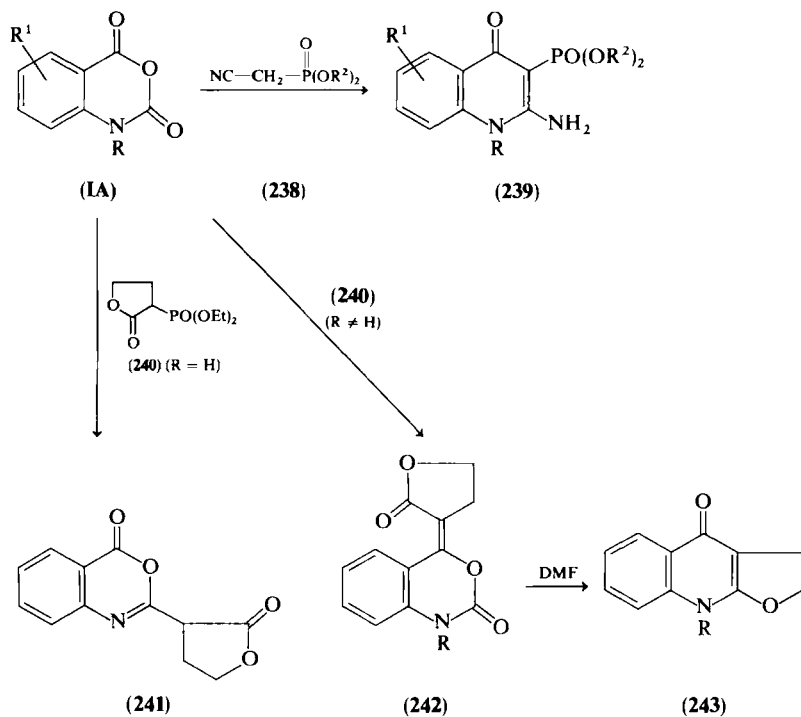
²⁸⁰ Sandoz Inc. (by G. E. Hardtmann and G. M. Coppola) U.S. Patent 4,070,468 (1978) [*CA* **88**, 136468 (1978)]; U.S. Patent 4, 124, 588 (1978) [*CA* **90**, 87664 (1979)].

²⁸¹ T. Minami, M. Matsumoto, H. Suganuma, and T. Agawa, *J. Org. Chem.* **43**, 2149 (1978).

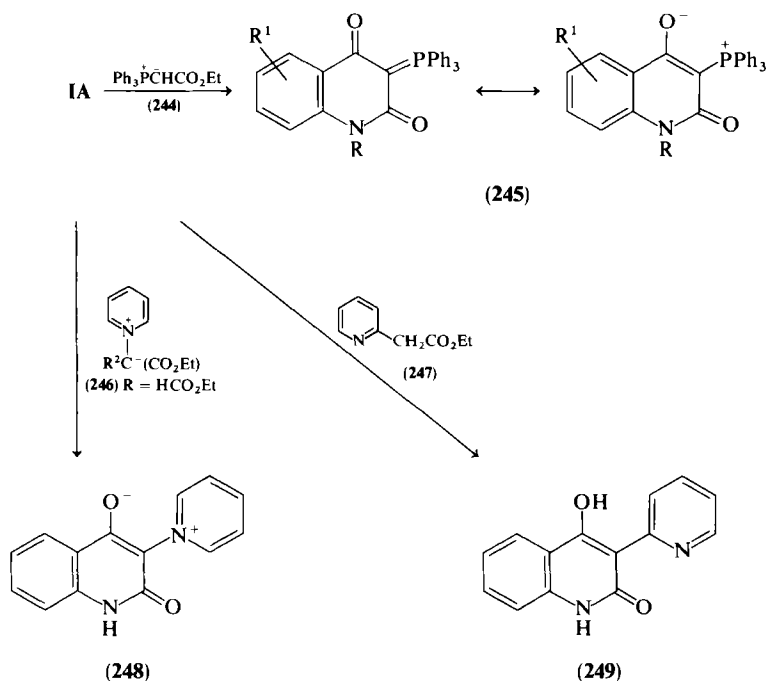
²⁸² D. T. Connor and M. von Strandman, *J. Org. Chem.* **38**, 1047 (1973).



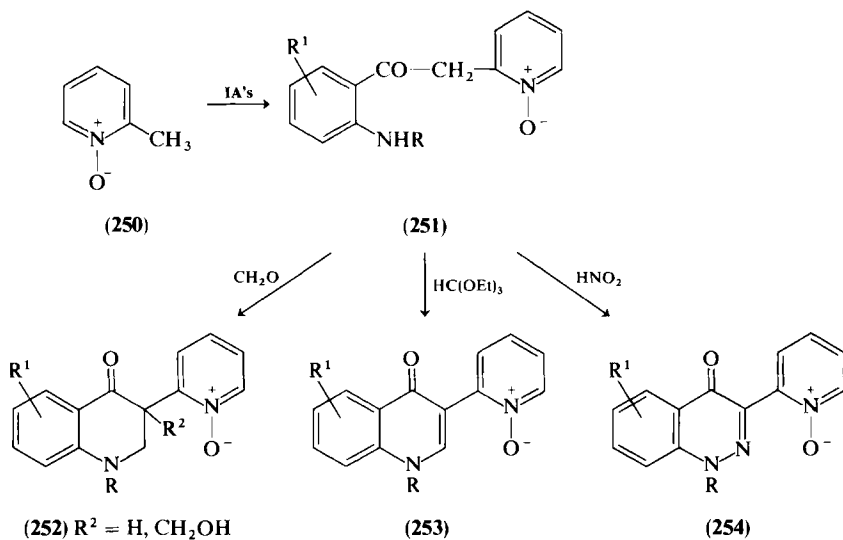
SCHEME 40



SCHEME 41



SCHEME 42

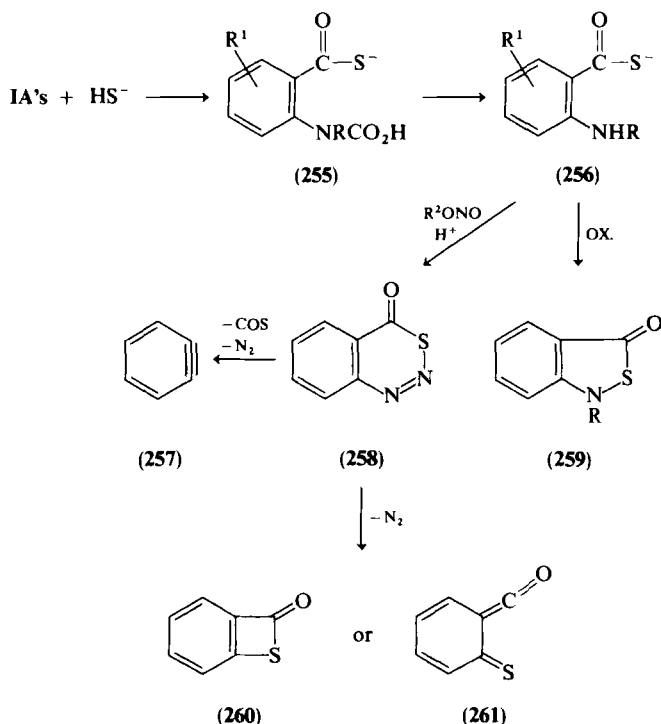


SCHEME 43

pyridinium ylid **248** is observed,²⁸³ while with ethyl 2-pyridylacetate (**247**) the isomer **249** is formed²⁸³ (Scheme 42). 2-Picoline-*N*-oxide (**250**) and IA furnish the acetophenone **251**,²⁸⁴ which is precursor of heterocycles **252**, **253**, and **254**, obtained with formaldehyde, orthoformate, or HNO_2 ²⁸⁵ (Scheme 43).

VI. Miscellaneous Reactions

IA and hydrogen sulfide react to form the isatoates **255** and their decarboxylated products **256**.^{110,111,286-288} Oxidation of **256** with iodine²⁸⁸ or H_2O_2 ^{286,287} leads to benzoisothiazolinones (**259**). Treatment of **256** with isoamyl nitrite or HNO_2 produces benzothiadiazinone (**258**),^{110,111} which



SCHEME 44

²⁸³ M. Hariri, Ph.D. Thesis, University of Graz, Austria (1976); T. Kappe, M. Hariri, and E. Pongratz, *Monatsh. Chem.* (in press).

²⁸⁴ D. T. Connor, P. A. Young, and M. von Strandman, *J. Heterocycl. Chem.* **14**, 139 (1977).

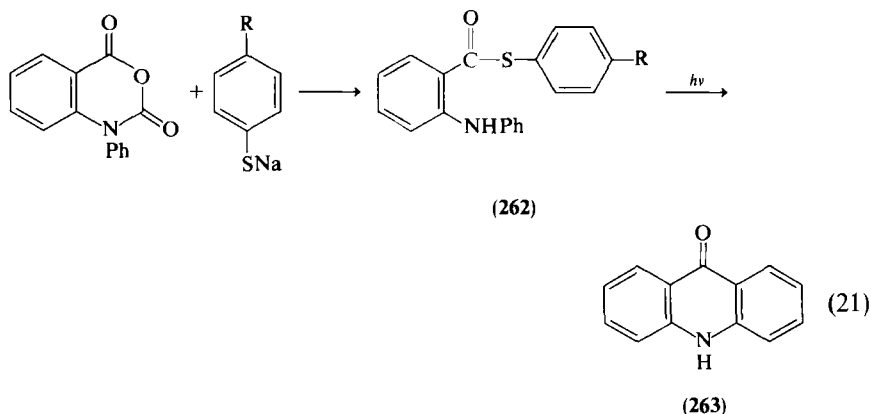
²⁸⁵ D. T. Connor, P. A. Young, and M. von Strandman, *J. Heterocycl. Chem.* **14**, 143 (1977).

²⁸⁶ A. H. Albert, R. K. Robins, and D. E. O'Brien, *J. Heterocycl. Chem.* **10**, 413 (1973).

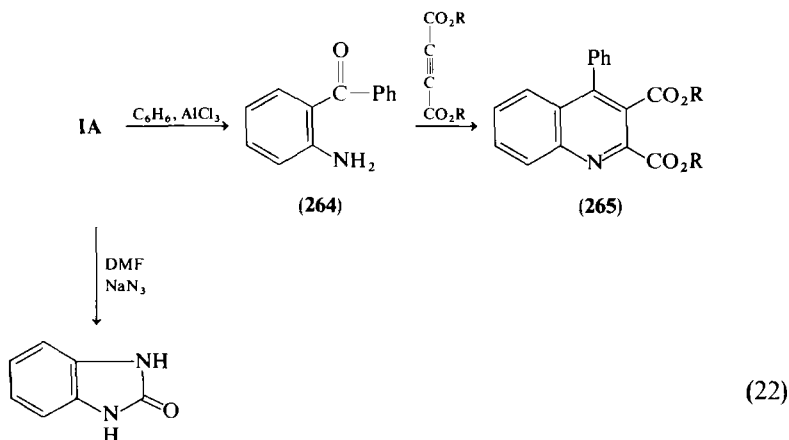
²⁸⁷ A. H. Albert, D. E. O'Brien, and R. K. Robins, *J. Heterocycl. Chem.* **15**, 529 (1978).

²⁸⁸ J. Faust and R. Mayer, *J. Prakt. Chem.* **318**, 161 (1976).

has been shown to decompose either via an aryne mechanism (trapped as trypticene) or via a mixture of aryne (**257**) and β -thiolactone (**260**) (or the isomeric ketene **261**), forming various dimers, adducts, and rearrangement products^{110,111} (Scheme 44). *N*-Phenyl IA and thiophenates react to give anthranilic acid thioesters (**262**), which undergo intramolecular photo-Friedel-Crafts reaction to give acridone (**263**)¹⁸ (Eq. 21). Friedel-Crafts



acylation of benzene by IA yields benzophenones (**264**),²⁸⁹ which can be cyclized with acetylenedicarboxylate to yield the quinoline **265**.²⁹⁰ IA and sodium azide in DMF give via Curtius rearrangement the five-membered benzimidazolone (**266**)²⁹¹ (Eq. 22).

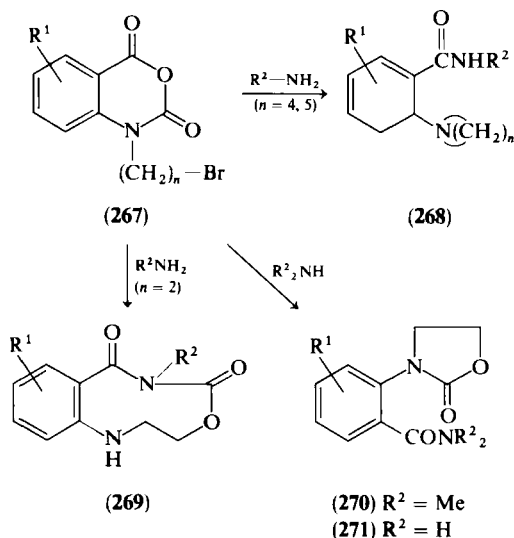


²⁸⁹ S. Statham, *J. Chem. Soc.*, 213 (1951); B. K. Misra, Y. R. Rao, and S. N. Mahapatra, *Indian J. Chem., Sect. B* **18**, 19 (1979); Sumitomo Chem. Co., Ltd. (by M. Akatsu, M. Yamamoto, K. Ishizumi, Y. Kume, M. Koshiba, S. Inaba, and H. Yamamoto), Japanese Kokai 72/34352 (1972) [*CA* **78**, 43047 (1972)].

²⁹⁰ E. C. Taylor and N. D. Heindel, *J. Org. Chem.* **32**, 1666 (1967).

²⁹¹ S. Marburg and P. A. Grieco, *Tetrahedron Lett.*, 1305 (1966).

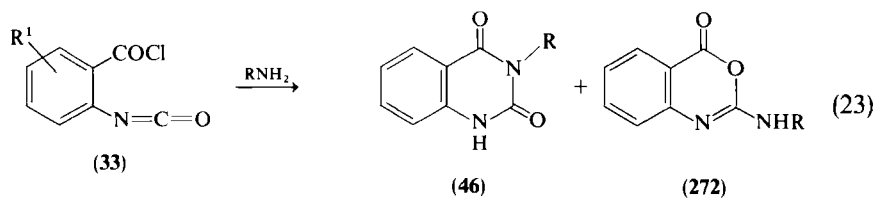
Reaction of *N*-haloalkyl IA (**267**) with amines does not stop at the anthranilamide step. With a four or five carbon chain the corresponding pyrrolidinyl or piperidinyl benzamides **268** are obtained. When *N*-bromoethyl IA (**267**; $n = 2$) was treated with methylamine, the benzoxadiazonine ring system (**269**) was formed, by trapping the carboxylate anion of the ring opened IA instead of CO_2 loss, followed by a rearrangement step. With dimethylamine the elusive intermediate of the former reaction, the oxazolidine **270**, was synthesized. Surprisingly, treatment with ammonia also afforded **271** and not the ring system of **269**. The possibility of an alternative mode of reaction with dimethylamine or ammonia via *o*-uramidobenzoic acids to yield a seven-membered ring system, was excluded by spectral data²⁹² (Scheme 45).



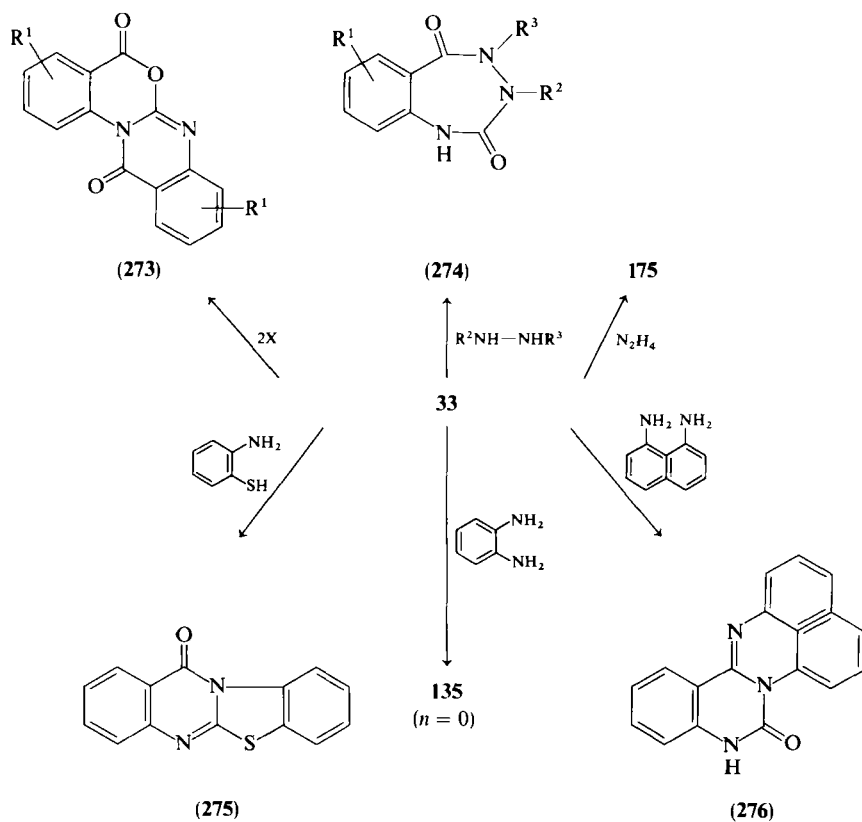
SCHEME 45

2-Isocyanatobenzoyl chloride (**33**; cf. Eq. 6) from IA and SOCl_2 , COCl_2 , or PCl_5 (Section I,B) was recently⁷⁵⁻⁷⁸ used as a reactive IA intermediate, giving a mixture of quinazolines (**46**) and benzoxazines (**272**) when reacted with primary amines^{77,78} (Eq. 23). Compound **33** dimerizes readily to quinazolinobenzoxazine (**273**)⁷⁹ and undergoes the same reactions as IA with substituted and unsubstituted hydrazines to give benzotriazepines (**274**) or 3-aminoquinazolines (**175**; cf. Scheme 8).⁷⁶ 2-Aminothiophenol treated with **33** furnishes **275**, and with *o*-phenylenediamine **135** (cf. Scheme 23; $n = 0$).⁷¹

²⁹² S. Barcza, G. M. Coppola, and M. J. Shapiro, *J. Heterocycl. Chem.* **16**, 439 (1979).



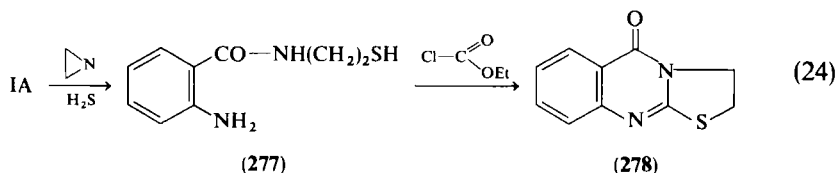
An analogous compound (276) was obtained with 1,8-diaminonaphthalene⁷¹ (Scheme 46).



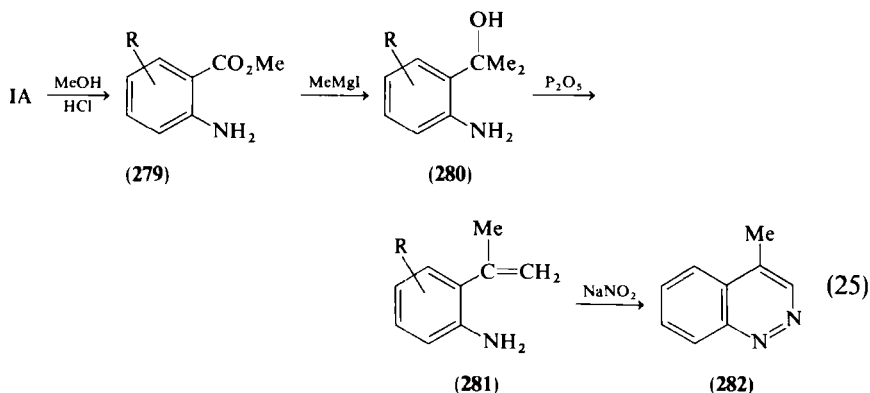
SCHEME 46

Reaction of IA with aziridine in the presence of hydrogen sulfide leads to the unstable intermediate 277, which produced the thiazoloquinazoline 278 with ethyl chloroformate (Eq. 24).²⁹³ Ring opening of IA to the anthranilate

²⁹³ N. Kaur, I. Singh, and H. Singh, *Indian J. Chem.* **1**, 308 (1963).



279 followed by a Grignard reaction to the alcohol **280** gives the cinnoline **282** by subsequent dehydration and diazotization (Eq. 25).²⁹⁴ *N*-Methyl-IA



(**24**) reacts with diethyl sodiophosphonate (**283**) to give dimethyl isoindigo (**284**).²⁹⁵ While acylations of IA with carboxylic, sulfonic, or phosphoric acid chlorides were not successful, reaction with the sulfenyl chloride **285** yields the *N*-acylated IA **286**.²⁹⁶ Indolylmagnesium bromide (**287**) and IA give the anthranilamide **288**, which undergoes cyclization with aqueous hydrochloric acid to give the indoloquinazolone **289** (Scheme 47).²⁹⁷

VII. Appendix Added in Proof

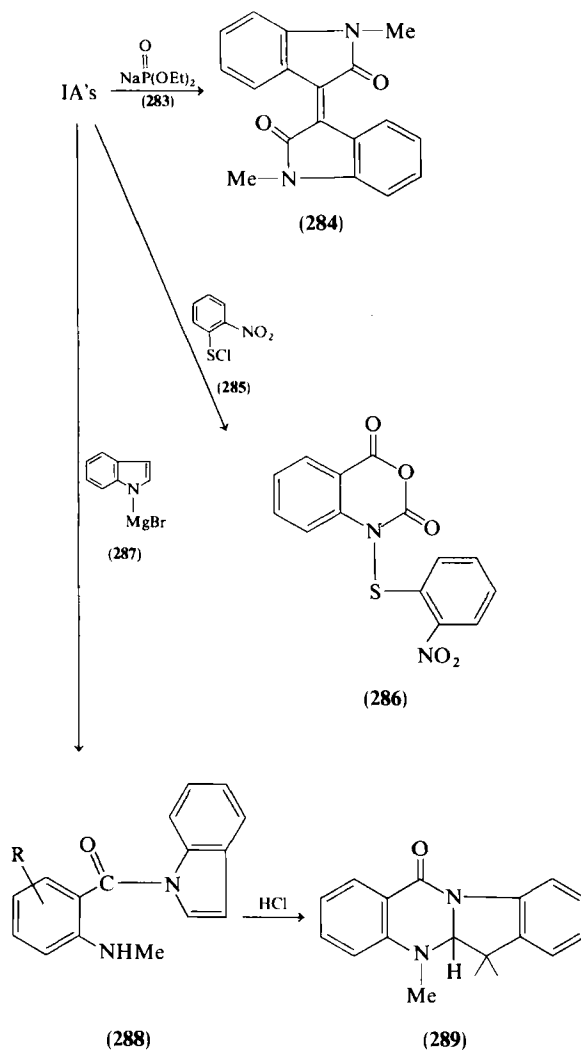
Since the original preparation of this review, additional reports have been published which give further information on the chemistry of IA's and their uses in heterocyclic synthesis. This appendix extends the referred literature,

²⁹⁴ R. N. Castle, K. Adachi, and W. D. Guither, *J. Heterocycl. Chem.* **2**, 459 (1965).

²⁹⁵ T. Minami, M. Matsumoto, and T. Agawa, *J.C.S., Chem. Commun.*, 1053 (1976).

²⁹⁶ H. R. Kricheldorf, *Angew. Chem.* **85**, 86 (1973).

²⁹⁷ E. E. Garcia, A. Arfai, and R. I. Fryer, *J. Heterocycl. Chem.* **7**, 1161 (1970).

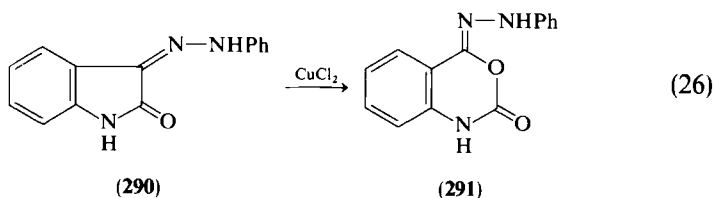


SCHEME 47

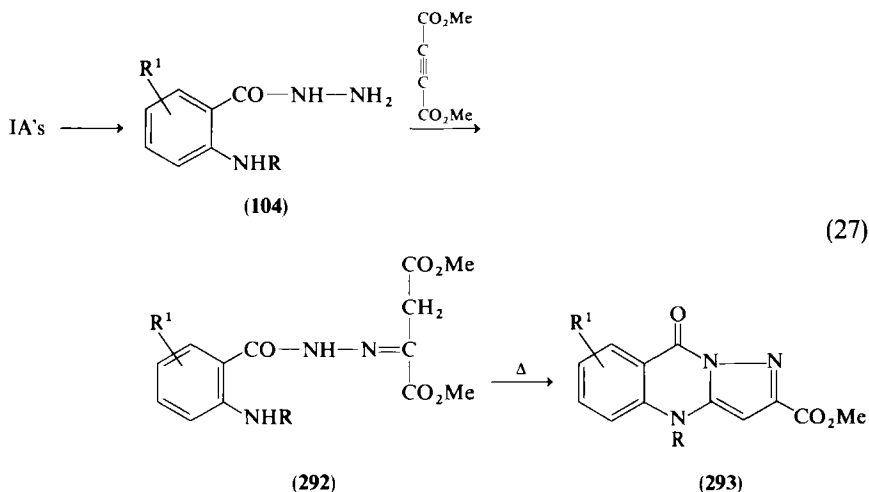
and reports which are similar to previously described reactions are added to the particular references. In the meantime, a review by G. M. Coppola on all aspects of IA chemistry has appeared.²⁹⁸

²⁹⁸ G. M. Coppola, *Synthesis*, 505 (1980).

The phenylhydrazone of IA (**291**), which is not available from IA directly, was synthesized via a ring expansion of the isatin **290** in the presence of CuCl_2 (Eq. 26).²⁹⁹ Reaction of the amino-substituted anthranilic hydrazide **104** with dimethyl acetylenedicarboxylate leads to the pyrazoloquinazalone



293 via the hydrazone **292** (Eq. 27),³⁰⁰ in contrast to the results obtained with amino-unsubstituted **104** (cf. Scheme 19). Dilithioacetophenone oxime

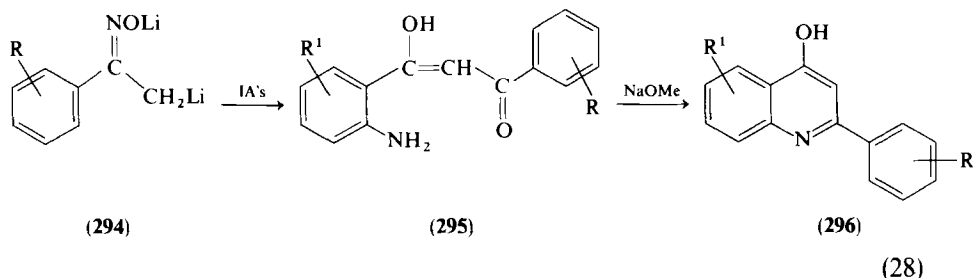


(**294**) was condensed with IA's to give the enols **295**, which cyclize to the quinolines **296** with sodium methoxide (Eq. 28).³⁰¹ When reacted with anthranilamide, IA afforded anthraniloyl anthranilamide (**297**), which undergoes cyclization with HNO_2 to give the triazinone **298**, which can be

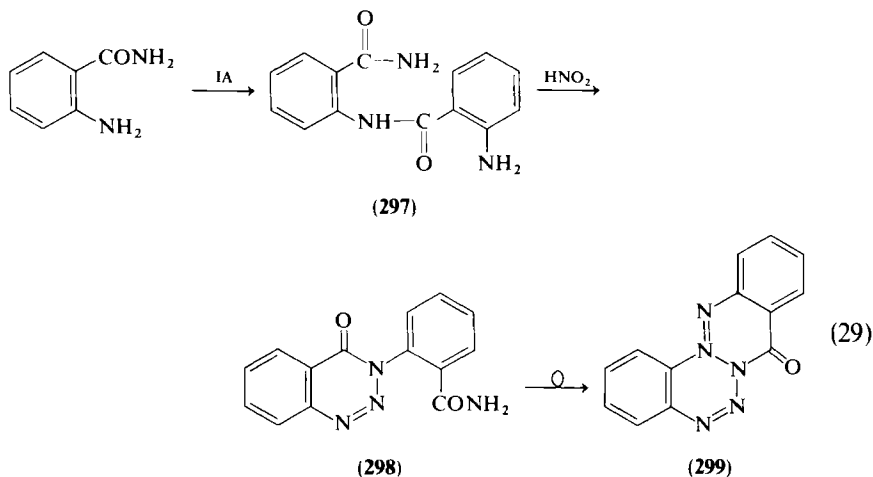
²⁹⁹ E. Sayed, H. E. Ashry, and Y. E. Kilany, *Indian J. Chem., Sect. B* **16**, 1036 (1978).

³⁰⁰ C. F. Beam, J. Brown, D. R. Dawkins, W. P. Fives, and N. D. Heindel, *J. Heterocycl. Chem.* **16**, 957 (1979).

³⁰¹ J. Brown, K. L. Sides, T. D. Fulmer, and C. F. Beam, *J. Heterocycl. Chem.* **16**, 1669 (1979).



used as *o*-aminobenzoylating agent. Treatment with bases yields the rearrangement product **299** (Eq. 29).³⁰²



Lactim ethers and thioethers (**300**) furnish condensed quinazolones **301** when interacted with IA.³⁰³ Ring opening of IA's to the corresponding anthranilic acids and reaction of its potassium salts with chloroacetone yields 2-indolyl ketones **302**.³⁰⁴ Potassium cyanide with *N*-substituted IA's produces iminoindolinones **303**, which were readily hydrolyzed to the corresponding isatins.³⁰⁵ Reaction of **303** to the spiroindoloquinazoline **304** takes place when KCN is treated with excess IA (Scheme 48).³⁰⁶ When

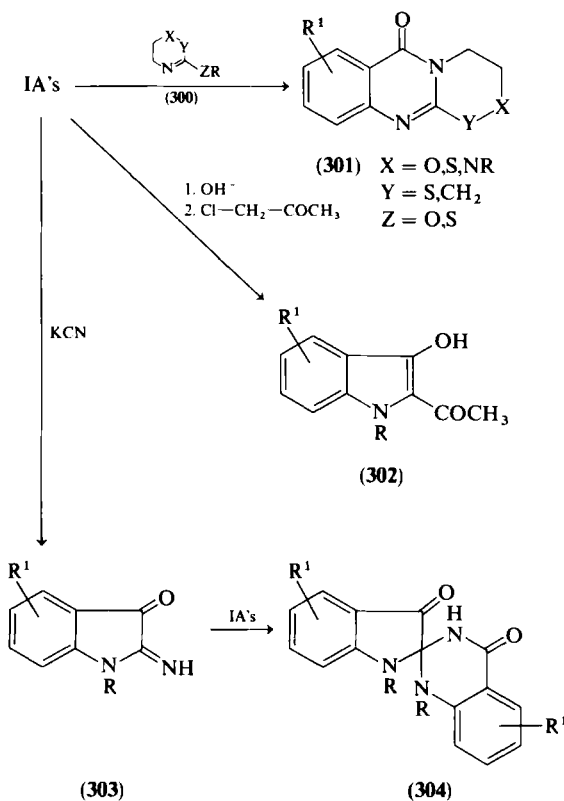
³⁰² F. D. Eddy, K. Vaughan, and M. F. G. Stevens, *Can. J. Chem.* **56**, 1616 (1978); C. Hinman and K. Vaughan, *Synthesis* 719 (1980).

³⁰³ K. Bhandari, V. Virmani, V. A. Murti, P. C. Jain, and N. Anand, *Indian J. Chem., Sect. B* **17**, 107 (1979).

³⁰⁴ P. C. Unangst, R. E. Brown, A. Fabian, and F. Fontsière, *J. Heterocycl. Chem.* **16**, 661 (1979).

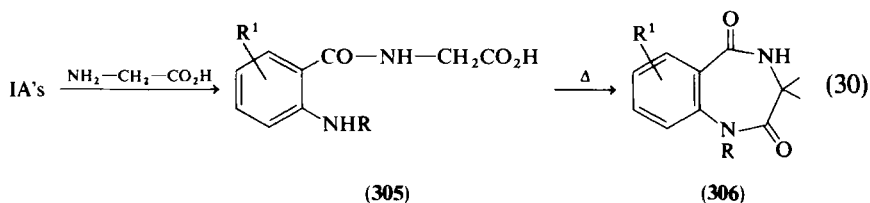
³⁰⁵ G. M. Coppola, *J. Heterocycl. Chem.* **16**, 827 (1979).

³⁰⁶ G. M. Coppola and R. E. Damon, *J. Heterocycl. Chem.* **16**, 1501 (1979).



SCHEME 48

glycine is allowed to react with IA's at low temperature, the hippuric acid **305** is isolated, which cyclizes at elevated temperatures yielding benzodiazepinediones **306** (Eq. 30).³⁰⁷



³⁰⁷ M. Gates, *J. Org. Chem.* **45**, 1675 (1980).

Reactions of Benzyne with Heterocyclic Compounds

MARTIN R. BRYCE AND JOHN M. VERNON

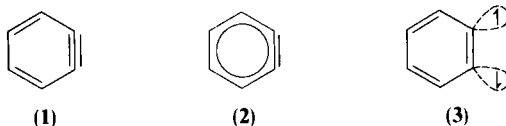
Department of Chemistry, University of York, Heslington, York, England

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I. Introduction

The term benzyne denotes *ortho*-benzyne, also known as 1,2-dehydrobenzene or in *Chemical Abstracts* as 1,3-cyclohexadien-5-yne. The last name is misleading, since benzyne lacks two *ortho* hydrogen atoms of benzene but not the stabilization associated with delocalization of double bonds. It is commonly represented by any of the structures 1–3. There is now a very

extensive chemistry of benzyne and of some of its substituted derivatives (arynes)^{1,2}; less use has been made of heterocyclic analogs of benzyne (hetarynes),³ and even less is known of *meta*- and *para*-benzyne isomers.



Observations of the UV absorption⁴ attributable to benzyne in the vapor phase, evidence from time-resolved mass spectrometry,⁵ and more recently of the IR spectrum⁶ of benzyne in a matrix at very low temperature leave no doubt as to the existence of such a transient intermediate. Its lifetime in solution is extended when benzyne is supported on a polymer phase.⁷ Results of competitive trapping experiments, when benzyne is generated from different precursors, and the classical experiments of Roberts *et al.* on cine-substitution in the amination of chlorobenzene confirm the formation of benzyne as an intermediate.^{8,9}

Apart from Hoffman's comprehensive treatment of the literature to 1966,¹ the numerous previous accounts of benzyne chemistry^{2,10,11} have given but scant attention to the reactions with heterocyclic compounds, which form the basis for the present chapter. We include selective coverage of relevant

¹ R. W. Hoffmann, "Dehydrobenzene and Cycloalkynes." Academic Press, New York, 1967, and references therein; R. W. Hoffmann, in "Chemistry of Acetylenes" (H. G. Viehe, ed.), Chapter 16. Dekker, New York, 1969.

² E. K. Fields, in "Organic Reactive Intermediates" (S. P. McManus, ed.), Chapter 7. Academic Press, New York, 1973.

³ H. J. den Hertog and H. C. van der Plas, in "Chemistry of Acetylenes" (H. G. Viehe, ed.), Chapter 17. Dekker, New York, 1969; T. Kauffmann and R. Wirthwein, *Angew. Chem., Int. Ed. Engl.* **10**, 20 (1971).

⁴ R. S. Berry, G. N. Spokes, and M. Stiles, *J. Am. Chem. Soc.* **84**, 3570 (1962).

⁵ R. S. Berry, J. Clardy, and M. E. Schafer, *J. Am. Chem. Soc.* **86**, 2738 (1964).

⁶ O. L. Chapman, K. Mattes, C. L. McIntosh, J. Pacansky, G. V. Calder, and G. Orr, *J. Am. Chem. Soc.* **95**, 6134 (1973); O. L. Chapman, C.-C. Chang, J. Kole, N. R. Rosenquist, and H. Tomioka, *ibid.* **97**, 6586 (1975).

⁷ P. Jayalekshmy and S. Mazur, *J. Am. Chem. Soc.* **98**, 6710 (1976).

⁸ R. Huisgen and R. Knorr, *Tetrahedron Lett.*, 1017 (1963).

⁹ J. D. Roberts, H. E. Simmons, L. A. Carlsmith, and C. W. Vaughan, *J. Am. Chem. Soc.* **75**, 3290 (1953); J. D. Roberts, D. A. Semenov, H. E. Simmons, and L. A. Carlsmith, *ibid.* **78**, 601 (1956).

¹⁰ R. Huisgen, in "Organometallic Chemistry" (H. Zeiss, ed.), Chapter 2. Van Nostrand-Reinhold, Princeton, New Jersey, 1960; R. Huisgen and J. Sauer, *Angew. Chem.* **72**, 91 (1960); J. Bunnett, *J. Chem. Educ.* **38**, 278 (1961); H. Heaney, *Chem. Rev.* **62**, 81 (1962); G. Wittig, *Angew. Chem., Int. Ed. Engl.* **4**, 731 (1965).

¹¹ T. L. Gilchrist and C. W. Rees, "Carbenes, Nitrenes, and Arynes," Chapter 8. Nelson, London, 1969; H. Heaney, *Essays Chem.* **1**, 95 (1970); N. S. Isaacs, "Reactive Intermediates in Organic Chemistry," Chapter 7. Wiley, New York, 1974.

reactions of substituted benzyne as well as some intramolecular reactions of particular interest involving arynes and heterocycles. A related area, the formation of heterocyclic products from reactions of benzyne with acyclic compounds, is mentioned only in passing.

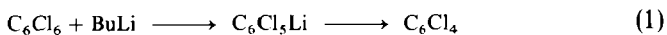
II. Methods of Benzyne Generation

This section describes the more important methods by which benzyne is generated for capture by heterocyclic compounds; it is not a comprehensive account of all known routes to benzyne (for which see Refs. 1 and 2). The importance of a variety of precursors and conditions for benzyne generation is to provide compatibility with heterocyclic co-reactants having widely differing properties.

A. FROM HALOGENOBENZENES

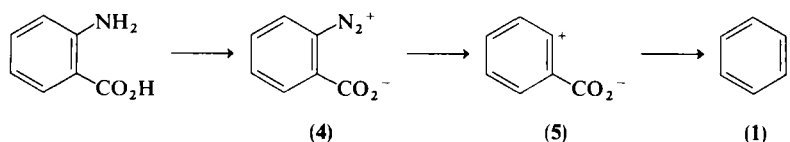
The use of sodium amide or potassium amide in liquid ammonia with bromo- or chlorobenzene leads inevitably to the capture of benzyne by its reaction with ammonia. However, the utility of bromo- or chlorobenzene as a benzyne precursor is extended to ethereal solvent systems by employing the conjugate base of a hindered secondary amine (diisopropylamine, 2,2,6,6-tetramethylpiperidine) which can be formed *in situ* from the amine and alkylolithium. Alternatively, butyllithium itself is used with the halogenobenzene, and pentafluorobenzene and butyllithium are the usual source of tetrafluorobenzyne. In all of these reactions the aryne is generated by decomposition of an *o*-halogenoaryl anion at temperatures below 0°C.

The formation of benzyne via $o\text{-FC}_6\text{H}_4\text{MgBr}$ from *o*-bromofluorobenzene and magnesium is closely related in mechanism to the base-induced eliminations, but the reaction conditions for the Grignard method (in refluxing tetrahydrofuran) are often more convenient. Benzyne is also produced from *o*-bromofluorobenzene and butyllithium, and hexachlorobenzene is the usual precursor for generation of tetrachlorobenzyne (Eq. 1).



B. ELIMINATION OF STABLE MOLECULES FROM *o*-DISUBSTITUTED BENZENES

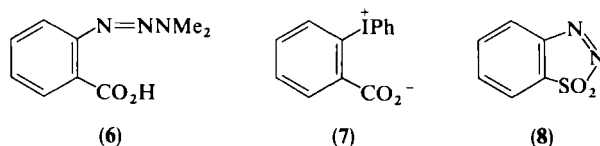
Aprotic diazotization of anthranilic acid, usually with pentyl nitrite, gives benzyne via the reaction sequence shown in Scheme 1. The intermediate benzenediazonium-2-carboxylate (**4**) is explosively unstable, but if it is isolated by performing the first step at 0°C it provides a clean source of benzyne



SCHEME 1

for reactions on a small scale.¹² Controlled decomposition of **4** or of its hydrochloride is accomplished above 40°C, commonly in ethers or chlorinated solvents at reflux temperature. A major advantage of this method is the absence of organometallic reagents and hence of strongly basic conditions. Stepwise decomposition of **4** is implied by the isolation of products in some cases which incorporate the structure of the intermediate (**5**). Substituted anthranilic acids are available as precursors for the corresponding arynes.

The triazene **6**, also derived from anthranilic acid, is more stable than **4** and can safely be stored in quantity. Benzyne, carbon dioxide, and dimethylamine are formed by decomposition of **6** in chlorobenzene at reflux temperature, or in benzene at 80°C in the presence of trichloroacetic acid.¹³ Benzyne is also produced on pyrolysis of diphenyliodonium-2-carboxylate (**7**) in various solvents at 160–220°C.¹⁴



C. THERMAL CLEAVAGE OF CYCLIC SYSTEMS

The analog of **4** with a sulfinate group replacing the carboxylate exists in the ring-closed form **8**; it decomposes in solution at 10°C to give benzyne, nitrogen, and sulfur dioxide.¹⁵ Oxidation of 1-aminobenzotriazole (**9**) with lead tetraacetate or other oxidants is another efficient source of benzyne via fragmentation of the intermediate nitrene **10**.¹⁶

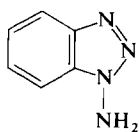
¹² L. Friedman and F. M. Logullo, *J. Am. Chem. Soc.* **85**, 1549 (1963); M. Stiles, R. G. Miller, and U. Burckhardt, *ibid.*, 1792; L. Friedman and F. M. Logullo, *J. Org. Chem.* **34**, 3089 (1969); F. M. Logullo, A. H. Seitz, and L. Friedman, *Org. Synth., Collect. Vol. 5*, 54 (1973).

¹³ J. Nakayama, O. Simamura, and M. Yoshida, *Chem. Commun.*, 1222 (1970); *Chem. Lett.*, 451 (1973).

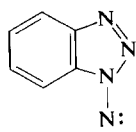
¹⁴ E. Le Goff, *J. Am. Chem. Soc.* **84**, 3786 (1962); F. M. Beringer and S. J. Huang, *J. Org. Chem.* **29**, 445 (1964).

¹⁵ G. Wittig and R. W. Hoffmann, *Angew. Chem.* **73**, 435 (1961); *Chem. Ber.* **95**, 2718 (1962); R. W. Hoffmann, W. Sieber, and G. Guhn, *ibid.* **98**, 3470 (1965).

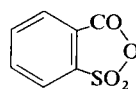
¹⁶ C. D. Campbell and C. W. Rees, *J. Chem. Soc. C*, 742, 752 (1969).



(9)

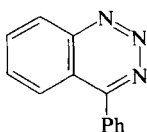


(10)

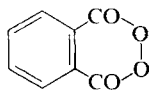


(11)

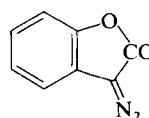
Benzyne is produced in the vapor phase by the fragmentation of phthalic anhydride and of *o*-sulfolic anhydride (**11**) at 690°C,¹⁷ also of 4-phenyl-1,2,3-benzotriazine (**12**),¹⁸ phthaloyl peroxide (**13**),¹⁹ and a variety of other cyclic systems at appropriately high temperatures. From the point of view of studying the reactions of benzyne with heterocycles, these methods are necessarily restricted in their application.



(12)



(13)



(14)

D. PHOTOCHEMICAL METHODS

Photochemical generation has proved particularly important for the characterization of benzyne by spectroscopic methods (Section I), but it is not much used to study the reactions of benzyne on a preparative scale. Benzyne is generated in an argon matrix at 8 K by photolysis of either **13** or **14**.⁶ Flash photolysis of **4** was employed by Berry *et al.* to obtain UV and mass spectral evidence of benzyne^{4,5}; and photolysis of 1,2,3-benzothiadiazole 1,1-dioxide (**8**),¹⁵ *o*-iodophenylmercury derivatives,¹⁹ and other compounds in solution also serves to generate benzyne.

III. Patterns of Benzyne Reaction

The reactions of benzyne are all additions to the formal triple bond of structure **1**. The variety of such reactions can be clarified in terms of open-chain additions and cycloadditions, although the isolated products are in many cases derived from secondary decomposition of such primary adducts. The isolation or postulation of cycloadducts in very few cases provides any

¹⁷ E. K. Fields and S. Meyerson, *Chem. Commun.*, 474 (1965); S. Meyerson and E. K. Fields, *ibid.*, 275 (1966).

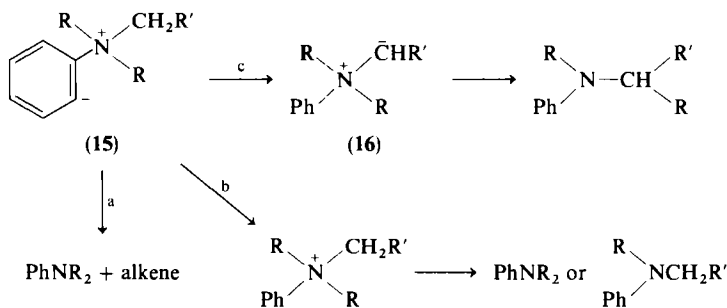
¹⁸ S. Bradbury, M. Keating, C. W. Rees, and R. C. Storr, *Chem. Commun.*, 827 (1971).

¹⁹ G. Wittig and H. F. Ebel, *Justus Liebigs Ann. Chem.* **650**, 20 (1961).

meaningful evidence about the concertedness of the cycloaddition step. On the contrary, a polar two-step mechanism is more likely for many of these reactions. The reactions of benzyne with heterocyclic compounds are often paralleled by reactions of acetylenedicarboxylic esters.²⁰

A. OPEN-CHAIN ADDITIONS

Benzyne reacts with compounds containing an X—H bond, where the atom X is nucleophilic or is made to be so by deprotonation; this gives an adduct PhX. A simple example is the formation of aniline when benzyne is generated in liquid ammonia. Heterocyclic secondary amines (e.g., piperidine) and other heterocyclic compounds containing NH groups (e.g., indoles) are converted into the corresponding *N*-phenyl derivatives. When benzyne reacts with a tertiary amine, the first-formed betaine **15** may undergo an intramolecular Hofmann elimination (e.g., if R' = Me), or it may be protonated and suffer displacement of one alkyl group from the quaternary ammonium ion, or an internal proton redistribution may give the ylid **16**, which then does a Stevens rearrangement (e.g., if R' = Ph).²¹ These reactions are shown as paths a, b, and c, respectively, in Scheme 2. Reactions of benzyne with sulfides are similar.²²



SCHEME 2

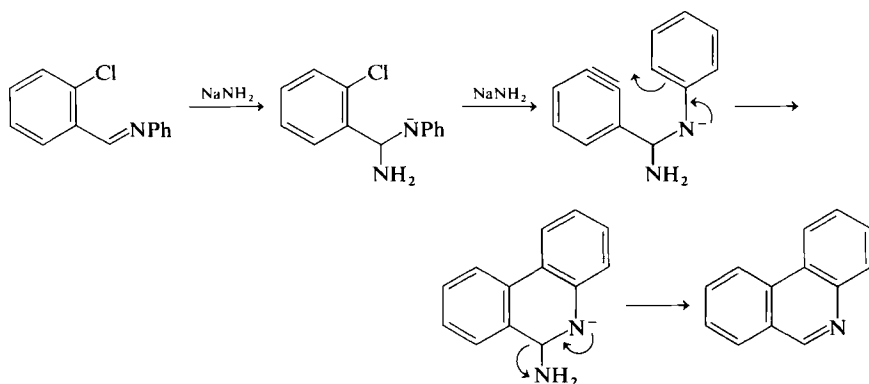
Benzyne also reacts with compounds containing nucleophilic carbon atoms such as enolates and aryl anions. Intramolecular nucleophilic addition to an aryne by the ortho ring carbon atom of another benzene ring substituted

²⁰ R. M. Acheson, *Adv. Heterocycl. Chem.* **1**, 125 (1963); R. M. Acheson and N. F. Elmore, *ibid.* **23**, 263 (1978).

²¹ G. Wittig and W. Merkle, *Chem. Ber.* **76**, 109 (1943); G. Wittig and E. Benz, *ibid.* **92**, 1999 (1959); cf. A. R. Lepley, *Prepr., Div. Pet. Chem., Am. Chem. Soc.* **14**, C43 (1969).

²² V. Franzen, H. I. Joschek, and C. Mertz, *Justus Liebigs Ann. Chem.* **654**, 82 (1962); H. Hellmann and D. Eberle, *ibid.* **662**, 188 (1963).

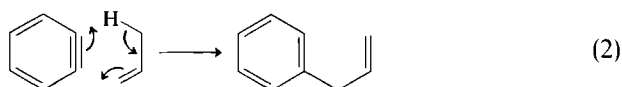
by an anionic group is the key step in a recent synthesis of phenanthridines, diazaphenanthrenes, and fused phenanthridines (Scheme 3).²³ Reactions of this type with heterocyclic substrates have been developed for the synthesis of some natural products (Section VII,C).



SCHEME 3

The formation of biphenyl by the formal insertion of benzyne into a C—H bond of benzene occurs in competition with cycloaddition processes, particularly when benzyne is generated at high temperatures in the vapor phase.¹⁷

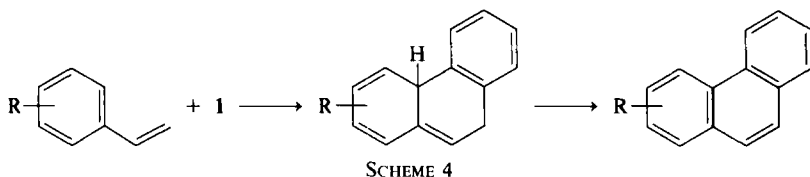
The “ene” reaction (Eq. 2) provides a nonpolar mechanism for open-chain addition of benzyne to compounds containing an allylic hydrogen atom. The implied migration of a double bond is not always apparent from the structure of the adduct. The “ene” reaction frequently occurs in competition with 1,2-cycloaddition; some examples are described in Refs. 1 and 2.



Aryne interconversion, involving the transfer to benzyne of two hydrogen atoms from adjacent positions of another aromatic compound, is apparently possible at high temperatures (see discussion of thiophen, Section V,B). 1,4-Abstraction of hydrogen atoms by benzyne is the most probable explanation of the aromatization of the Diels–Alder adducts of benzyne and some styrene derivatives under the relatively mild conditions used for benzyne generation from *o*-bromofluorobenzene or benzenediazonium-2-carboxylate (4) (Scheme 4).²⁴

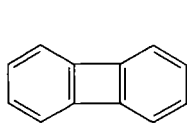
²³ S. V. Kessar, *Acc. Chem. Res.* **11**, 283 (1978), and references therein.

²⁴ W. Davies and J. R. Wilmshurst, *J. Chem. Soc.*, 4079 (1961); S. F. Dyke, A. R. Marshall, and J. P. Watson, *Tetrahedron* **22**, 2515 (1966); E. Wolthuis and W. Cady, *Angew. Chem., Int. Ed. Engl.* **6**, 555 (1967).

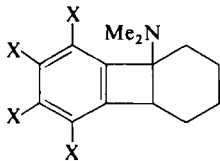


B. 1,2-CYCLOADDITIONS

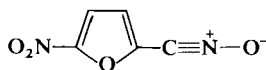
The dimerization of benzyne to form biphenylene (**17**) is an example of 1,2-cycloaddition which occurs in particularly high yield when benzyne is generated from 1-aminobenzotriazole (**9**)¹⁶ but also by other methods, if the concentration or reactivity of other potential benzyne traps is low.¹² Nucleophilic addition of enolates to benzyne is followed by closure to a four-membered ring which is frequently re-opened in a subsequent reaction step.²⁵ Similarly, benzyne and tetrahalogenbenzyne react with enamines to give adducts containing a benzocyclobutene structure (e.g., **18**).²⁶ Analogous benzyne adducts are isolable in a few cases from indoles and pyrroles (Section V,C), and 1,2-cycloaddition of benzyne followed by rearrangement of the primary adduct is postulated to explain certain other reactions with heterocycles.



(17)



(18) X = H, F, Cl



(19)

C. 1,3-CYCLOADDITIONS

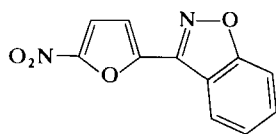
Benzyne can be trapped in 1,3-dipolar cycloaddition reactions provided that the 1,3-dipolar species is sufficiently stable under the conditions necessary for benzyne generation. As an illustration of this, benzyne reacts with the nitrile oxide group in preference to the furan ring of compound **19**, whereby adduct **20** is obtained.²⁷ Benzyne and the nitron **21** give adduct **22**,²⁸ and

²⁵ P. Caubère, *Acc. Chem. Res.* **7**, 301 (1974), and references therein.

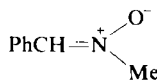
²⁶ M. E. Kuehne, *J. Am. Chem. Soc.* **84**, 837 (1962); J. P. N. Brewer, H. Heaney, S. V. Ley, and T. J. Ward, *J. C. S., Perkin I*, 2688 (1974); H. Heaney and S. V. Ley, *ibid.*, 2693.

²⁷ T. Sasaki and T. Yoshioka, *Bull. Chem. Soc. Jpn.* **42**, 826 (1969).

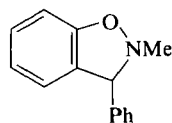
²⁸ R. Huisgen and R. Knorr, *Naturwissenschaften* **48**, 716 (1961); H. Seidl, R. Huisgen, and R. Knorr, *Chem. Ber.* **102**, 904 (1969).



(20)



(21)



(22)

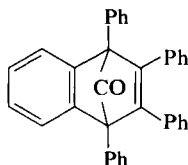
similar reactions with azides or with diazoketones produce benzotriazole or indazole derivatives, respectively, in high yield.^{29,30}

1,3-Dipolar cycloaddition reactions lead to heterocyclic products, but our concern will be only with those in which a hetero-ring is already present in reactions involving benzyne. Heterocyclic *N*-oxides (Section IX) and meso-ionic heterocycles (Section VI,B) provide most examples of this type, although there are some cases of apparent 1,3-cycloaddition of benzyne to heterocycles in which no formal 1,3-dipole is identifiable.

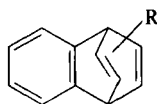
D. 1,4-CYCLOADDITIONS

Benzyne is reactive as a dienophile and provides many examples of Diels-Alder addition. It is efficiently trapped by anthracene to give triptycene and by tetracyclone to give 1,2,3,4-tetraphenylnaphthalene via decarbonylation of adduct **23**, reactions which are commonly used to quantify the formation of benzyne under given conditions.

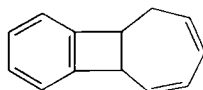
1,4-Cycloaddition of benzyne and of tetrahalogenobenzenes also occurs with simple monocyclic benzenoid compounds, and at higher temperatures (e.g., if benzyne is generated from phthalic anhydride) adducts such as **24** may rearomatize by elimination of acetylene. 1,4-Cycloadducts of benzyne and heterocyclic substrates are sometimes isolable, but frequently they too react further by a variety of pathways to give secondary products (Sections V, VI, and VII).



(23)



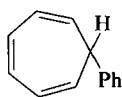
(24)



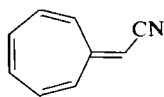
(25)

²⁹ G. A. Reynolds, *J. Org. Chem.* **29**, 3733 (1964); W. Ried and M. Schön, *Chem. Ber.* **98**, 3142 (1965); R. Huisgen, R. Knorr, L. Möbius, and G. Szeimies, *ibid.*, 4014.

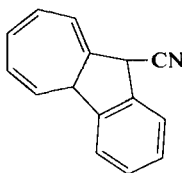
³⁰ W. Ried and M. Schön, *Justus Liebigs Ann. Chem.* **689**, 141 (1965); T. Yamazaki and H. Shechter, *Tetrahedron Lett.*, 4533 (1972); C. Tuchscherer, M. Bruch, and D. Rewicki, *ibid.*, 865 (1973); T. Yamazaki, G. Baum, and H. Shechter, *ibid.*, 4421 (1974).



(26)



(27)



(28)

Nucleophilic addition of dienolates to substituted benzyne is followed by closure of a six-membered ring to form naphthalene derivatives.³¹

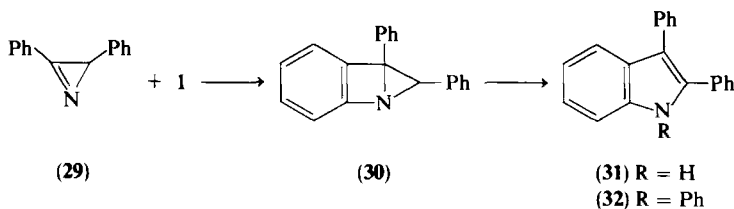
E. 1,5-, 1,6-, AND 1,8-CYCLOADDITIONS

1,5-Cycloaddition of benzyne occurs in two cases of homo-Diels–Alder additions (e.g., to norbornadiene) reported in Ref. 1.

A 1,6-cycloaddition was wrongly claimed to occur with benzyne and cycloheptatriene. The structure of the cycloadduct is reliably established as **25**, and the isomer **26** derived from an “ene” reaction was also obtained.³² 1,8-Cycloaddition of benzyne occurs with 8-cyanoheptafulvene (**27**) to give **28**.³³ It is clearly possible to envisage similar reactions occurring with heterocyclic compounds, although none has yet been reported.

IV. Reactions with Three- and Four-Membered Ring Systems

2,3-Diphenyl-1-azirine (**29**) and benzyne yield the 1:1 adduct **31** (50%) and 1:2 adduct **32** (14%).³⁴ The formation of these indoles can be explained by assuming 1,2-cycloaddition of benzyne, reorganization of the strained intermediate **30**, and some N-phenylation of **31** by further reaction with benzyne.



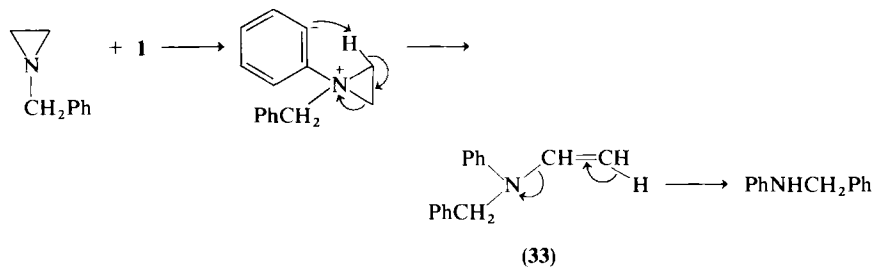
³¹ P. G. Sammes and T. W. Wallace, *J. C. S., Perkin I*, 1377 (1975).

³² I. Tabushi, H. Yamada, Z. Yoshida, and H. Kuroda, *Tetrahedron Lett.*, 1093 (1974); L. Lombardo and D. Wege, *ibid.*, 3981.

³³ M. Oda and Y. Kitahara, *Bull. Chem. Soc. Jpn.* **43**, 1920 (1970).

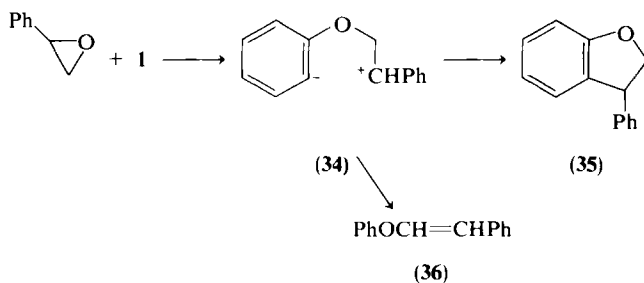
³⁴ V. Nair and K. H. Kim, *J. Org. Chem.* **40**, 3784 (1975).

N-Benzylaniline (14%) was obtained from *N*-benzylaziridine and benzyne (from fluorobenzene and butyllithium).³⁵ The strongly basic conditions may cause the elimination of acetylene from an intermediate *N*-vinyaniline (33) as outlined in Scheme 5.



SCHEME 5

Styrene oxide and benzyne are reported to give the 1:1 adducts **35** and **36** (9% and 6% yield, respectively), both derived from the same intermediate **34**.³⁶ However, propene oxide is apparently unreactive to benzyne, since its use is advocated to react with the hydrogen chloride which is released when benzyne is generated by decomposition of *o*-carboxybenzenediazonium chloride (Section II,B).^{37, 37a, b}



Although benzyne is formed by decomposition of 4-phenyl-1,2,3-benzotriazine (**12**) above 500°C,¹⁸ 2-phenylbenzazete (**37**) has been isolated on a cold finger by flash vacuum pyrolysis of **12** at 420–450°C.³⁸ A by-product of this reaction is 10-phenylacridine (**38**), which may result from addition of

³⁵ A. G. Giumanini, *J. Org. Chem.* **37**, 513 (1972).

³⁶ M. Stiles and A. Haag, personal communication, 1964, reported in Ref. 1.

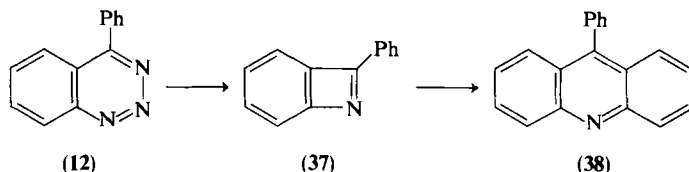
³⁷ L. Friedman, personal communication, 1965, reported in Refs. 1 and 2; cf. experimental procedure described in Refs. 37a, b.

^{37a} G. Kaupp, J. Perreten, R. Leute, and H. Prinzbach, *Chem. Ber.* **103**, 2288 (1970).

^{37b} N. Dennis, A. R. Katritzky, and M. Ramaiah, *J. C. S., Perkin I*, 1506 (1975).

³⁸ B. M. Adger, M. Keating, C. W. Rees, and R. C. Storr, *J. C. S., Chem. Commun.*, 19 (1973).

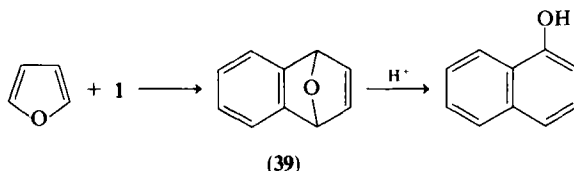
benzyne across the C=N bond of **37**, although an alternative route involving formation and decomposition of a dimer of **37** was shown to give **38** as the temperature was raised from 195 K.



V. Reactions with Five-Membered Ring Systems Containing One Heteroatom

A. FURANS AND BENZOFURANS

The very efficient reaction of furan with benzyne, discovered by Wittig and Pohmer was the earliest example of benzyne behaving as a dienophile.³⁹ Formation of the oxygen-bridged adduct **39** and its acid-catalyzed isomerization into 1-naphthol are often used diagnostically for the detection of benzyne generated by new pathways.



The corresponding Diels–Alder adducts have been prepared from substituted furans, including methylfurans and tetraphenylfuran.^{40–43} A previous review⁴⁴ summarizes some interesting features of the aromatization under acidic conditions of derivatives of structure **39** containing methyl groups at the bridgehead positions.^{42,45} Addition of hydrogen to the isolated double

³⁹ G. Wittig and L. Pohmer, *Angew. Chem.* **67**, 348 (1955); *Chem. Ber.* **89**, 1334 (1956).

⁴⁰ E. Wolthuis, *J. Org. Chem.* **26**, 2215 (1961).

⁴¹ L. F. Fieser and M. J. Haddadin, *Can. J. Chem.* **43**, 1599 (1965).

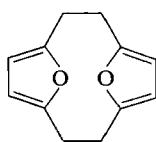
⁴² E. Wolthuis, B. Bossenbroek, G. DeWall, E. Geels, and A. Leegwater, *J. Org. Chem.* **28**, 148 (1963); W. Tochtermann, G. Stubenrauch, and H. Zimmermann, *Chem. Ber.* **108**, 2510 (1975).

⁴³ G. Wittig and E. Knauss, *Chem. Ber.* **91**, 895 (1958).

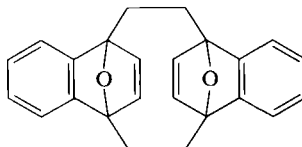
⁴⁴ L. J. Kricka and J. M. Vernon, *Adv. Heterocycl. Chem.* **16**, 87 (1974).

⁴⁵ M. Fetizon and N. T. Anh, *Bull. Soc. Chim. Fr.*, 3208 (1965); cf. R. W. Franck and K. Yanagi, *Tetrahedron Lett.*, 1789 (1967); *J. Org. Chem.* **33**, 811 (1968).

bond of **39** and cycloadditions of diazomethane, phenyl azide, and dienes have been reported³⁹⁻⁴¹; pyrolysis of the 2,3-dihydro derivative or the tetracyclone adduct of **39** affords the unsubstituted benzo[*c*]furan (**42**).^{41,46}

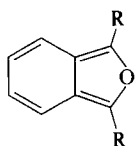


(40)

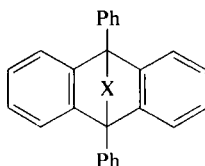


(41)

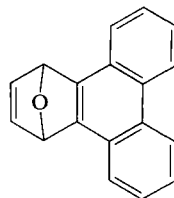
Benzyne adds to the furanophane **40** to give successively 1:1 and 2:1 adducts; the latter (**41**) probably has the anti configuration.⁴⁷ 1,3-Diphenylbenzo[*c*]furan (**43**) is also an efficient trap for benzyne, and the adduct **44** gives 9,10-diphenylantracene in diglyme at 162°C, or on reduction with zinc and acetic acid.^{14,48} Some other instances of the loss of the bridging oxygen atom of furan adducts occur when the aryne in question is generated from an *o*-aryl dihalide by the action of lithium amalgam, e.g., the isolation of triphenylene (77%) instead of the expected adduct **46** from capture of 9,10-dehydrophenanthrene by furan.⁴⁹



(42) R = H
(43) R = Ph



(44) X = O
(45) X = S



(46)

Tetrahalogenobenzyne have been trapped with furan to give adducts analogous to **39** containing F, Cl, Br, or I; the tetrachloro derivative of **44** has also been prepared.^{50,51} The adducts obtained from furan and a number of other arynes are documented in Ref. 1.

⁴⁶ U. E. Wiersum and W. J. Mijs, *J. C. S., Chem. Commun.*, 347 (1972).

⁴⁷ L. A. Kapicak and M. A. Battiste, *J. C. S., Chem. Commun.*, 930 (1973).

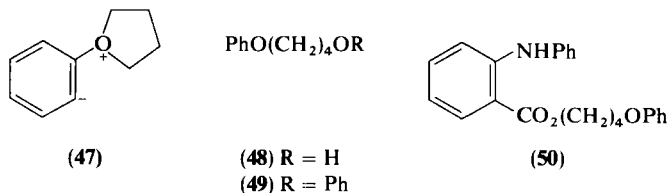
⁴⁸ G. Wittig, E. Knauss, and K. Niethammer, *Justus Liebigs Ann. Chem.* **630**, 10 (1960).

⁴⁹ G. Wittig, W. Uhlenbrock, and P. Weinhold, *Chem. Ber.* **95**, 1692 (1962); cf. T. Kauffmann and F.-P. Boettcher, *ibid.*, 949; T. Kauffmann and K. Udluft, *Angew. Chem., Int. Ed. Engl.* **2**, 45 (1963).

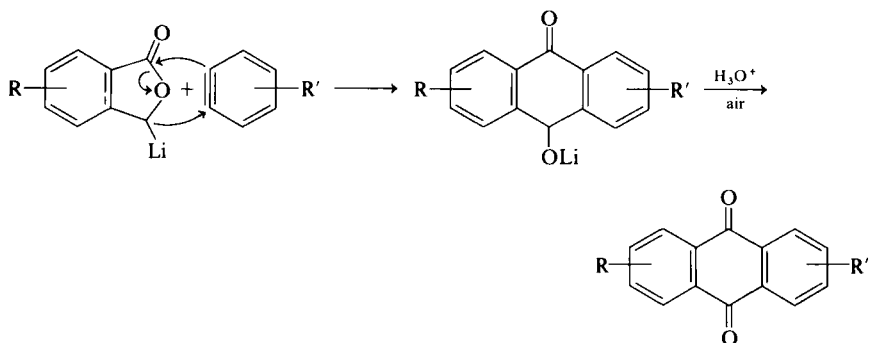
⁵⁰ P. L. Coe, R. Stephens, and J. C. Tatlow, *J. Chem. Soc.*, 3227 (1962); cf. B. Hankinson, H. Heaney, and R. P. Sharma, *J. C. S., Perkin I*, 2372 (1972).

⁵¹ H. Heaney and J. M. Jablonski, *J. Chem. Soc. C*, 1895 (1968); H. Heaney, K. G. Mason, and J. M. Sketchley, *ibid.*, 567 (1971).

Tetrahydrofuran is widely employed as a solvent for reactions involving benzyne, yet it has been shown to be attacked by benzyne (from anthranilic acid diazotized *in situ*) to give products derived via the betaine **47**.⁵² In the presence of water **48** and **49** are obtained (23% and 8%, respectively), whereas under anhydrous conditions the main product is **50** (17%) by reaction of **47**



with anthranilic acid and further N-phenylation by benzyne. A ring-opened product, 4-(tetrachlorophenoxy)butyl tetrachlorobenzoate, is reported from the related reaction of tetrahydrofuran with tetrachlorobenzyne (from tetrachloroanthranilic acid).⁵² Tetrahydrofuran is also a component in a remarkable single-stage synthesis of anthracene (63%); the interpretation is that benzyne (from bromobenzene and lithium 2,2,6,6-tetramethylpiperidide) adds to the lithium enolate of acetaldehyde, which is produced from tetrahydrofuran under strongly basic conditions.⁵³



SCHEME 6

A recent synthesis of anthraquinones involves the base-catalyzed addition of phthalides to arynes (generated from the corresponding aryl bromide and lithium diisopropylamide), as outlined in Scheme 6.⁵⁴

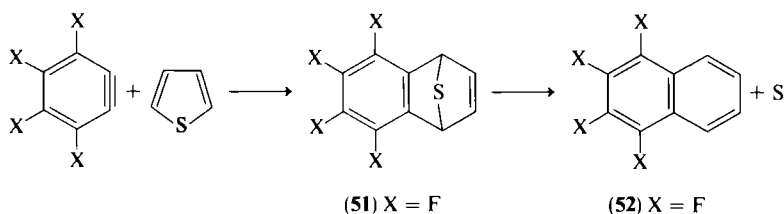
⁵² E. Wolthuis, B. Bouma, J. Modderman, and L. Sytsma, *Tetrahedron Lett.*, 407 (1970); G. I. Fray and R. G. Saxton, *Tetrahedron* **34**, 2663 (1978).

⁵³ I. Fleming and T. Mah, *J. C. S., Perkin I*, 964 (1975).

⁵⁴ P. G. Sammes and D. J. Dodsworth, *J. C. S., Chem. Commun.*, 33 (1979).

B. THIOPHEN AND BENZOTHIOPHENS

Although thiophen fails to react with benzyne at ordinary temperatures, it is attacked by the more reactive dienophile, tetrafluorobenzyne (from pentafluorophenyllithium at 15°C), to give 1,2,3,4-tetrafluoronaphthalene (**52**) (26%). Transient NMR absorptions attributable to the bridgehead and vinylic hydrogen atoms of the intermediate Diels–Alder adduct **51** were observed.⁵⁵ A minor product of the same reaction, pentafluorothiophenol, is known to be formed from pentafluorophenyllithium and sulfur; the sulfur in this instance comes from the aromatization of **51** (Scheme 7). 1,3-Dichloro-2,4-difluoronaphthalene (36%) was obtained similarly from the mixed halobenzyne and thiophen.⁵⁶ Tetrafluorobenzyne and tetrachlorothiophen gave the corresponding tetrachlorotetrafluoronaphthalene in only low yield.⁵⁵



SCHEME 7

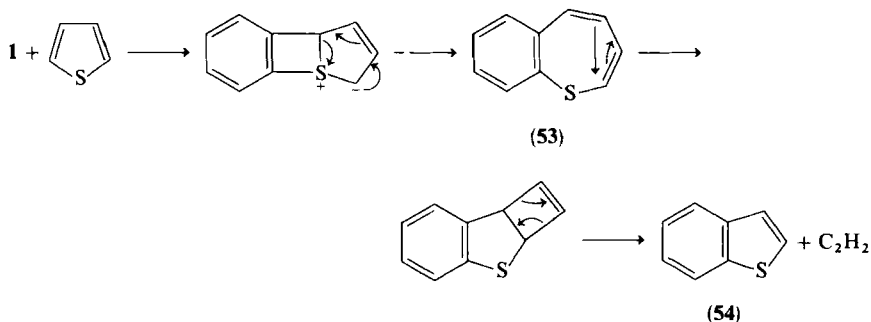
Benzyne (from pyrolysis of phthalic anhydride) reacts with thiophen at 690°C to give mainly naphthalene, benzo[*b*]thiophen (**54**), 2- and 3-phenylthiophens, and bithienyl.⁵⁷ The bithienyl (probably the 2,2'-isomer) is also formed from thiophen alone under the same conditions. The phenylthiophens arise by insertion of benzyne into C—H bonds of thiophen. The source of naphthalene is most likely to be via a Diels–Alder reaction (Scheme 7, X = H), and Fields and Meyerson assume a mechanism involving initially 1,2-cycloaddition of benzyne to a C—S bond of thiophen to account for the formation of **54** (Scheme 8).^{2,57,58} However, there is no evidence to support such a route, which seems unconvincing, not least because benzo[*b*]thiepin (**53**)

⁵⁵ D. D. Callander, P. L. Coe, and J. C. Tatlow, *Chem. Commun.*, 143 (1966); D. D. Callander, P. L. Coe, J. C. Tatlow, and A. J. Uff, *Tetrahedron* **25**, 25 (1969).

⁵⁶ S. Hayashi and N. Ishikawa, *Yuki Gosei Kagaku Kyokai Shi* **28**, 533 (1970) [*CA* **73**, 45241 (1970)].

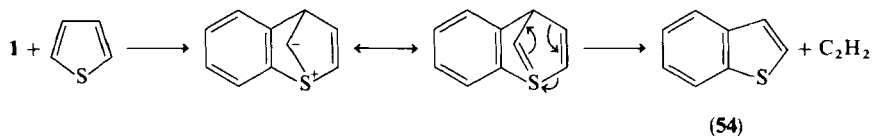
⁵⁷ E. K. Fields and S. Meyerson, *Chem. Commun.*, 708 (1966); *Prepr., Div. Petrol. Chem., Am. Chem. Soc.* **12**, 57 (1967); in "Organosulfur Chemistry" (M. J. Jansen, ed.), p. 143. Wiley, New York, 1967; *J. Org. Chem.* **34**, 2475 (1969).

⁵⁸ E. K. Fields and S. Meyerson, *Adv. Phys. Org. Chem.* **6**, 1 (1968).



SCHEME 8

very readily loses sulfur rather than acetylene.⁵⁹ We therefore prefer a simpler mechanism involving 1,3-cycloaddition of benzyne to thiophen as shown in Scheme 9.^{59a}



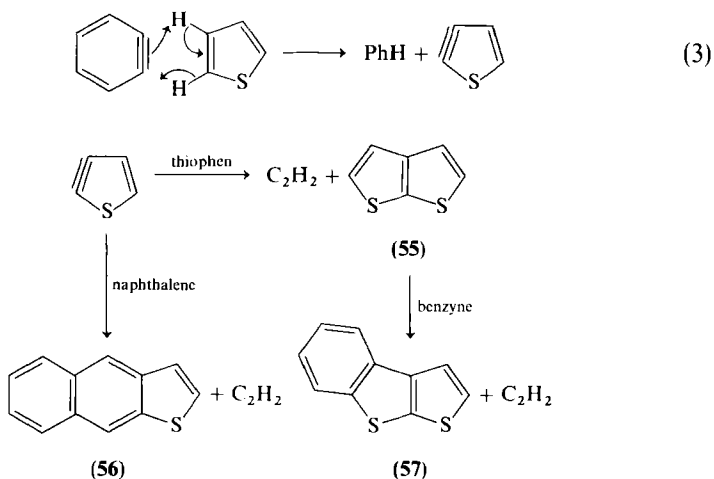
SCHEME 9

Minor products from benzyne and thiophen include the thiophthen **55**, the benzothiophthen **57**, and naphtho[2,3-*b*]thiophen (**56**). Their formation is ingeniously explained in terms of the aryne interconversion to give 2,3-dehydrothiophen (Eq. 3), followed by reactions of the latter as outlined in Scheme 10. We consider both the reaction of 2,3-dehydrothiophen with thiophen and that of **55** with benzyne in Scheme 10 to involve 1,3-cycloadditions analogous to that shown in Scheme 9 instead of 1,2-cycloadditions as originally suggested.^{57,58} As required by Eq. (3), benzene was also detected among the pyrolysis products from phthalic anhydride and thiophen, neither of which originally contained any benzene.

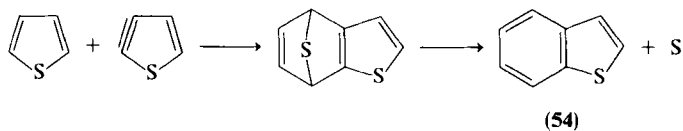
2,3-Dehydrothiophen could also be involved in an alternative route leading to **54** (Scheme 11)⁵⁸; however, this is unlikely to be important, since tetrachlorobenzyne (from pyrolysis of tetrachlorophthalic anhydride) and thio-

⁵⁹ V. J. Traynelis, Y. Yoshikama, J. C. Sih, and L. J. Miller, *J. Org. Chem.* **38**, 3978 (1973); cf. V. J. Traynelis, in "Seven-membered Heterocyclic Compounds containing Oxygen and Sulfur" (A. Rosowsky, ed.), Chapter 11, Wiley, New York, 1972; R. M. Acheson, "An Introduction to the Chemistry of Heterocyclic Compounds," 3rd ed., Chapter 10, and references therein, Wiley, New York, 1976.

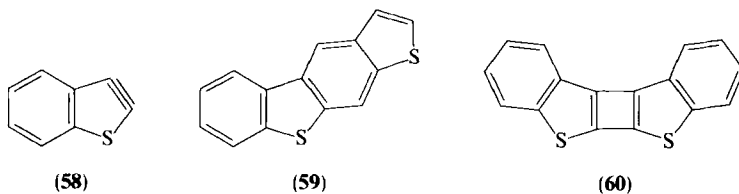
^{59a} Cf. D. Del Mazza and M. G. Reinecke, *J. C. S., Chem. Commun.*, **124** (1981).



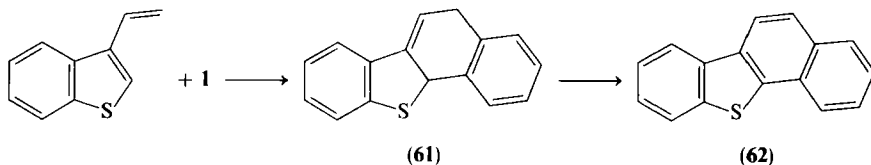
phen give tetrachlorobenzo[*b*]thiophen as well as tetrachloronaphthalene, tetrachlorophenylthiophen, and tetrachlorobenzothiophen.



The same authors have also reported the reactions of other arynes with thiophene and the reactions of benzyne with **54**.^{57,58} They present speculative reaction mechanisms to account for the formation of products, which in many cases are imperfectly identified from mass spectra alone. For example, although they acknowledge an inability to distinguish between anthracene and phenanthrene,⁵⁸ they claim, in the same article, both of these as products of distinct reactions of benzyne with **54**. Two minor products are claimed to be **59** and **60**, respectively, and to provide evidence for the intervention of 2,3-dehydrobenzo[*b*]thiophen (**58**).



3-Vinylbenzo[*b*]thiophen and benzyne (from *o*-bromofluorobenzene) afford **62** (13%); dehydrogenation of the 1:1 adduct **61** is possibly induced by attack of benzyne.⁶⁰ Formation of the 1:1 adduct **45** (14%), from benzyne and 1,3-diphenylbenzo[*c*]thiophen (**143**) is accompanied by some desulfurization to give 9,10-diphenylanthracene (9%)⁴⁸; **45** also loses sulfur at 250°C.



C. PYRROLES, INDOLES, AND ISOINDOLES: NAPHTHALEN-1,4-IMINES AND ANTHRACEN-9,10-IMINES

A previous review⁴⁴ deals with the addition of benzyne to pyrroles and isoindoles to give nitrogen-bridged structures. Although pyrrole itself and benzyne (from *o*-FC₆H₄MgBr) give only 2-phenylpyrrole, pyrrolmagnesium iodide and benzyne afford the naphthalen-1,4-imine **67** in low yield.⁶¹ Simple pyrroles substituted on nitrogen by an electron-withdrawing group (CO₂R, SO₂Ar) react with benzyne to give adducts of the same type (e.g., **68**) in good yield,^{37a,62} since the N-substituent inhibits further attack of benzyne at the nitrogen atom. From *N*-benzyl-, *N*-methyl-, and *N*-phenylpyrrole the corresponding Diels–Alder adduct **63** is isolable, at best, in low yield; it may rearrange to a 1-naphthylamine derivative **64** or its further reaction with benzyne leads to the formation of rearranged 1:2 adducts (**65** or **66**) as shown in Scheme 12.^{61,63}

Except in cases where the substituent on nitrogen is electron-withdrawing (CO₂Me), the nitrogen-bridged adducts derived from 1,2,5-trisubstituted pyrroles are particularly labile, and they rearrange to 2-naphthylamine derivatives (e.g., **70** \rightarrow **75**) which are the isolable products of reactions with benzyne.^{64,65} The similar rearrangement **71** \rightarrow **76** is induced by treatment with acid, but reduction or hydrolysis of the NCO₂Me group of **71** is possible under basic conditions to give **72** or **73**, respectively.⁶⁵ The preferred route to naphthalen-1,4-imines unsubstituted on nitrogen, such as **73** and **80**,

⁶⁰ T. G. Corbett and Q. N. Porter, *Aust. J. Chem.* **18**, 1781 (1965).

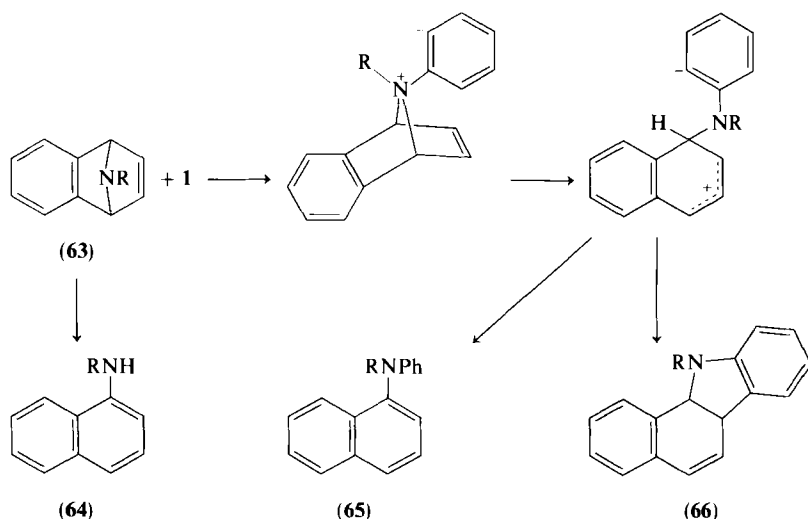
⁶¹ G. Wittig and B. Reichl, *Chem. Ber.* **96**, 2851 (1963).

⁶² L. A. Carpino and D. E. Barr, *J. Org. Chem.* **31**, 764 (1966).

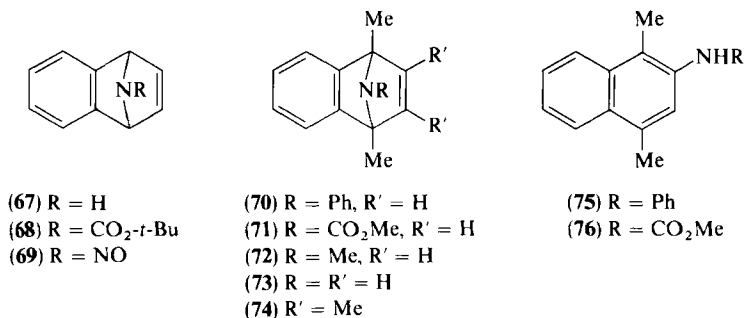
⁶³ G. Wittig and W. Behnisch, *Chem. Ber.* **91**, 2358 (1958).

⁶⁴ E. Wolthuis, D. V. Jagt, S. Mels, and A. DeBoer, *J. Org. Chem.* **30**, 190 (1965).

⁶⁵ J. M. Vernon, M. Ahmed, and J. M. Moran, *J. C. S., Perkin I*, 1084 (1977).



SCHEME 12

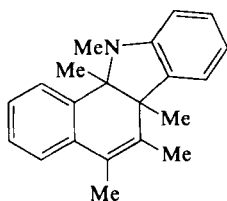


involves addition of benzyne to *N*-trimethylsilylpyrroles, when the protecting group is removed during an aqueous work-up procedure.⁶⁶ Some other transformations of *N*-substituents, which have been accomplished with preservation of the acid-sensitive naphthalen-1,4-imine ring system, include **68** → **67**, **67** → **69**, and **80** → **81**^{62,66}; other examples are reported in Ref. 44.

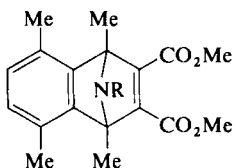
From pentamethylpyrrole and benzyne the rearranged 1:2 adduct **77** was obtained; but from some other pentasubstituted pyrroles the naphthalen-1,4-imines **74** could be isolated, and two of these (R = *n*-Bu, cyclo-C₆H₁₁)

⁶⁶ P. S. Anderson, M. E. Christy, G. F. Lundell, and G. S. Ponticello, *Tetrahedron Lett.*, 2553 (1975); P. S. Anderson, M. E. Christy, E. L. Engelhardt, G. F. Lundell, and G. S. Ponticello, *J. Heterocycl. Chem.* **14**, 213 (1977).

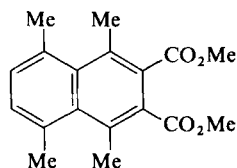
were then converted into benzo[*a*]carbazole derivatives analogous to **77** by a subsequent reaction with benzyne.⁶⁷



(77)



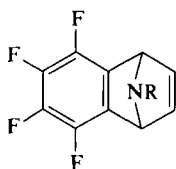
(78)



(79)

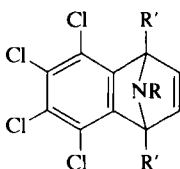
Naphthalene is formed from the *N*-nitrosoimine **69** at 45°C via a cheletropic reaction.⁶² In some instances benzyne induces deamination of naphthalen-1,4-imines, since naphthalene was a by-product of the reaction of benzyne with *N*-methylpyrrole,⁶³ and the naphthalene ester **79** is produced by reaction of **78** with benzyne.⁶⁸ An indication of the fate of the extruded nitrogen-containing fragment is provided by the identification of *N*-methylcarbazole as a product of the reaction of **82** with benzyne.

Diels–Alder adducts (e.g., **81**–**84**) have been prepared from *N*-substituted pyrroles with tetrafluoro- and tetrachlorobenzyne.^{55,66,69,70} These adducts are less readily isomerized to naphthylamine derivatives and less prone to react further with benzyne. A minor product of the reaction of tetrachlorobenzyne with *N*-*tert*-butylpyrrole is the 1,2-cycloadduct **85** (2%), for which



(80) R = H

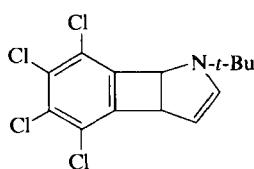
(81) R = Me



(82) R = Me, R' = H

(83) R = *t*-Bu, R' = H

(84) R = R' = Me



(85)

there are precedents in enamine chemistry.²⁶ Compound **81** undergoes rearrangement and fragmentation reactions on pyrolysis⁷¹; **83** cleaves to acetylene and an isoindole above 200°C.⁷⁰ Deamination of **81** to tetrafluoro-

⁶⁷ E. Wolthuis and A. DeBoer, *J. Org. Chem.* **30**, 3225 (1965); E. Wolthuis, W. Cady, R. Roon, and B. Weidenaar, *ibid.* **31**, 2009 (1966).

⁶⁸ L. J. Kricka and J. M. Vernon, *J. C. S., Perkin I*, 766 (1973).

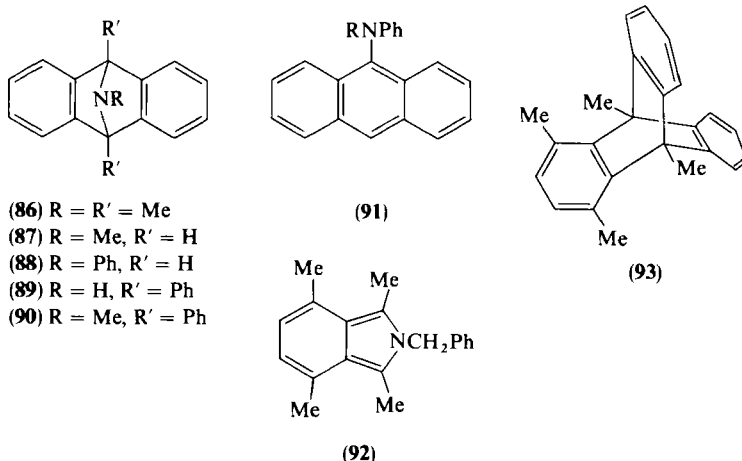
⁶⁹ G. W. Gribble, N. R. Easton, and J. T. Eaton, *Tetrahedron Lett.*, 1075 (1970).

⁷⁰ M. Ahmed and J. M. Vernon, *J. C. S., Chem. Commun.*, 462 (1976); J. M. Vernon, M. Ahmed, and L. J. Kricka, *J. C. S., Perkin I*, 837 (1978).

⁷¹ P. L. Coe and A. J. Uff, *Tetrahedron* **27**, 4065 (1971); H. Heaney and S. V. Ley, *J. C. S., Perkin I*, 2698 (1974).

naphthalene (**52**) occurs on treatment with *m*-chloroperbenzoic acid,⁷² and **52** and heterocyclic products are obtained by reaction of **81** with dimethyl acetylenedicarboxylate.⁷⁰

Anthracen-9,10-imines (e.g., **86–90**) are obtained by addition of benzyne (from various precursors) to isoindoles,^{48,68,73} and the scope of this synthesis has recently been extended to include the use of substituted benzyne and some new isoindoles.⁷⁴ 1,3-Diphenyl-2*H*-isoindole affords **89** (43%) without



N-phenylation. The further reaction of **87** and **88** with benzyne to give 9-aminoanthracene derivatives **91** (cf. the mechanism outlined in Scheme 12) is blocked by the presence of substituents at the bridgehead positions as in **86**. Anthracene (9%) is also produced from the reaction of **87** with benzyne,⁴⁸ and the formation of the tetramethyltritypycene **93** from benzyne and the isoindole **92** is attributed to a similar deamination of an intermediate anthracen-9,10-imine.⁶⁸ Deamination of **86** and **87** is more conveniently accomplished by treatment with hydrogen peroxide.⁷²

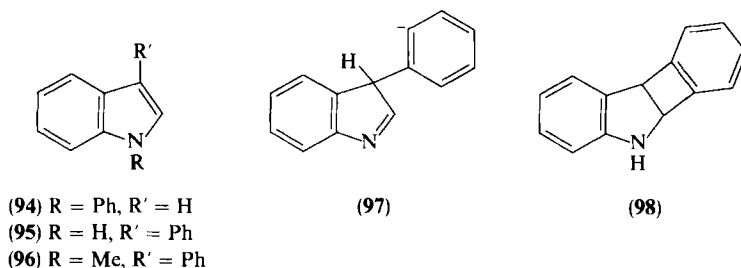
The reaction of indole with benzyne has been studied only under strongly basic conditions in which indole is first converted into its lithium or sodium derivative. Indol-1-yllithium and benzyne (from *o*-FC₆H₄MgBr) gave the tetracyclic 1:1 adduct **98** as the main product (8%) together with small

⁷² G. W. Gribble, R. W. Allen, P. S. Anderson, M. E. Christy, and C. D. Colton, *Tetrahedron Lett.*, 3673 (1976).

⁷³ J. C. Emmett and W. Lwowski, *Tetrahedron* **22**, 1011 (1966); R. Harrison, H. Heaney, and P. Lees, *ibid.* **24**, 4589 (1968).

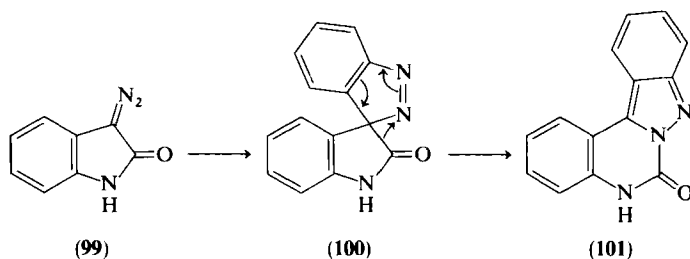
⁷⁴ P. S. Anderson, M. E. Christy, C. D. Colton, W. Halczenko, G. S. Ponticello, and K. L. Shepard, *J. Org. Chem.* **44**, 1519 (1979); Merck and Co., Inc., German Patent 2,521,519 [CA **84**, 59189 (1976)].

amounts of *N*-phenylindole (**94**) and 3-phenylindole (**95**).⁷⁵ 1-Methyl-3-phenylindole (**96**) (4%) was formed from *N*-methylindole and benzyne under

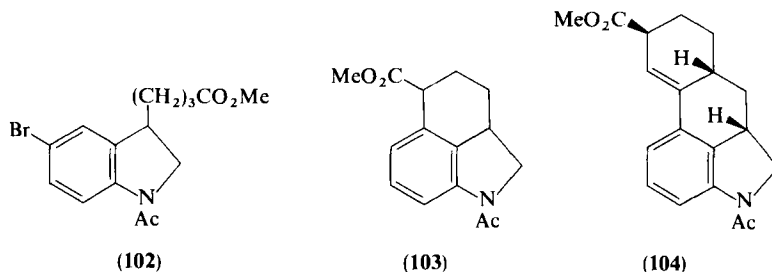


the same conditions. Indole and benzyne (from bromobenzene and sodium amide in liquid ammonia) gave more of the two phenylindoles (20%) but none of **98**, because protonation of the intermediate anion (**97**) was faster than its cyclization to **98**.

1,3-Cycloaddition of benzyne to 3-diazooxindole (**99**) led, via rearrangement of the spiro adduct **100**, to the condensed indazole derivative **101** (91%), the structure of which was confirmed by an independent synthesis.⁷⁶



Julia *et al.* have employed intramolecular reactions of arynes generated from indoline derivatives for closure of a six-membered ring linking the 3- and 4-positions. Thus, **103** is obtained from **102** by treatment with sodium



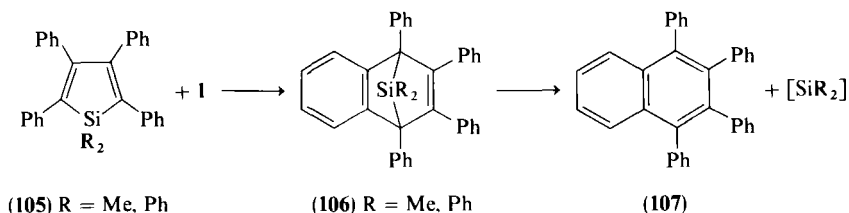
⁷⁵ M. E. Kuehne and T. Kitagawa, *J. Org. Chem.* **29**, 1270 (1964).

⁷⁶ T. Yamazaki and H. Shechter, *Tetrahedron Lett.*, 1417 (1973).

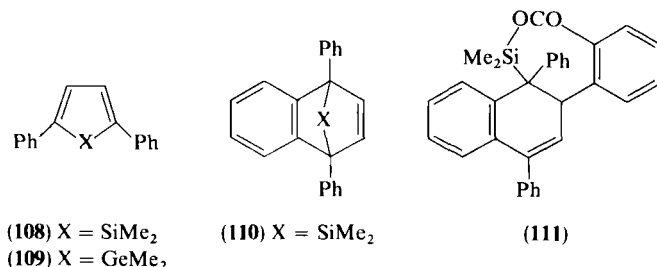
amide in liquid ammonia, and a similarly conceived synthesis gives the lysergic acid analog **104**.⁷⁷

D. SILICON AND GERMANIUM HETEROCYCLES

1,4-Silicon-bridged adducts (**106**) were obtained in good yield from fully substituted siloles (**105**) and benzyne (from diazotization of anthranilic acid).⁷⁸ Pyrolysis of **106** at 300°C gave tetraphenyl-naphthalene (**107**), and the complementary silylene fragment was captured in the presence of diphenylacetylene. The corresponding 1:1 adduct **110** from the silole **108** and benzyne (from 1-aminobenzotriazole and lead tetraacetate) is stable in solution at -50°C, but it decomposes below room temperature to give 1,4-diphenyl-naphthalene.⁷⁹ The difference in thermal stability of **106** and **110** may be due to the greater steric hindrance involved in the formation of **107** from **106**.



If benzyne was generated instead from *o*-carboxybenzenediazonium chloride in the presence of **108**, the remarkable siloxepine **111** was formed (>70%); its structure was confirmed by X-ray diffraction.⁷⁹ It was shown that the intermediate 1:1 adduct **110** reacts with benzenediazonium-2-carboxylate (**4**) at a lower temperature than is required for the decomposition **4** → **5** → **1** (Scheme 1); this step includes the formation of the strong Si—O bond, and subsequent loss of nitrogen and cyclization lead to **111**. The germanium analog of **111** was similarly obtained from **109**.



⁷⁷ M. Julia, F. Le Goffie, J. Igolen, and M. Baillarge, *Bull. Soc. Chim. Fr.*, 1071 (1968); *Tetrahedron Lett.*, 1569 (1969).

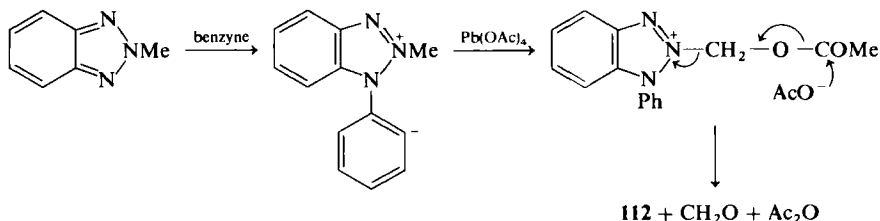
⁷⁸ H. Gilman, S. G. Cottis, and W. H. Atwell, *J. Am. Chem. Soc.* **86**, 1596, 5584 (1964).

⁷⁹ T. J. Barton, A. J. Nelson, and J. Clardy, *J. Org. Chem.* **37**, 895 (1972).

VI. Five-Membered Ring Systems with Two or More Heteroatoms

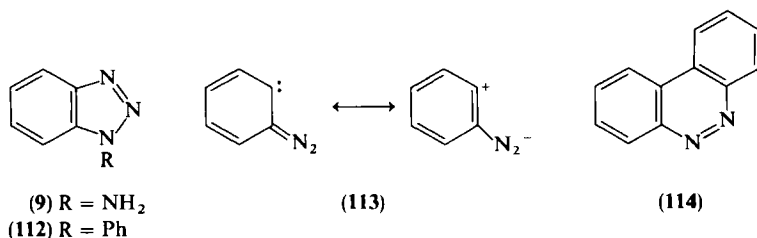
A. HETEROCYCLES CONTAINING A FORMAL DIENE SYSTEM

Imidazole, benzimidazole, and benzotriazole give *N*-phenyl derivatives in low yield with benzyne^{16,80}; 1-methylbenzotriazole understandably fails to react.⁸¹ In contrast, 2-methylbenzotriazole reacts with benzyne (from oxidation of **9** with lead tetraacetate) to give 1-phenylbenzotriazole (**112**) (22%).⁸¹ The mechanism suggested to account for incorporation of benzyne and oxidative removal of the *N*-methyl group is outlined in Scheme 13; formaldehyde may be further oxidized under these conditions. 2-Benzylbenzotriazole and benzyne under the same conditions afforded **112** and benzoic acid.⁸¹ When benzyne was generated from **4** instead, it reacted with 2-methylbenzotriazole to give phenazine (2%) and no **112**.⁸²



SCHEME 13

Benzo[*c*]cinnoline (**114**) (3%) was separated from a complex mixture of colored products obtained from the oxidation of **9** with active manganese dioxide; formation of **114** suggests the stepwise loss of nitrogen, **10** → **113** → **1**, and 1,4-dipolar cycloaddition of benzyne to **113**.¹⁶ Oxidation of **9** with (diacetoxyiodo)benzene gave azobenzene (4%), 1-phenylbenzotriazole (**112**)

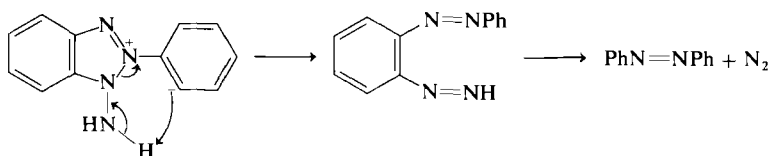


⁸⁰ A. F. Pozharskii, T. M. Meleshko, and A. M. Simonov, *Khim. Geterotsikl. Soedin.*, 473 (1966) [*CA* **65**, 8895 (1966)].

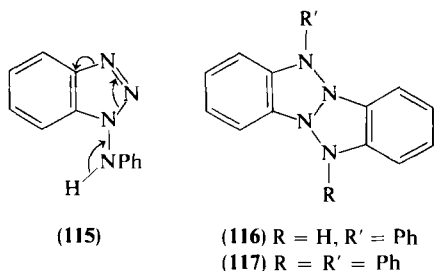
⁸¹ C. D. Campbell and C. W. Rees, *J. Chem. Soc. C*, 748 (1969).

⁸² C. D. Campbell, C. W. Rees, M. R. Bryce, M. D. Cooke, P. Hanson, and J. M. Vernon, *J. C. S., Perkin I*, 1006 (1978).

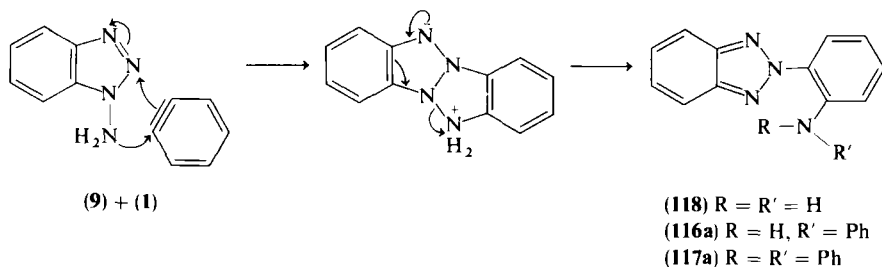
(3%), and two other heterocyclic products believed to be **116** and **117** (20% together); azobenzene and **112** were also obtained using "nickel peroxide" as the oxidant.¹⁶ Formation of **112** implies the production of both benzyne and benzotriazole from **9** under these conditions, and formation of azobenzene was explained in terms of an initial attack of benzyne at the 2-position of **9** (Scheme 14). An alternative possibility is that attack of benzyne at the exocyclic nitrogen atom could lead via **115** to azobenzene.



SCHEME 14

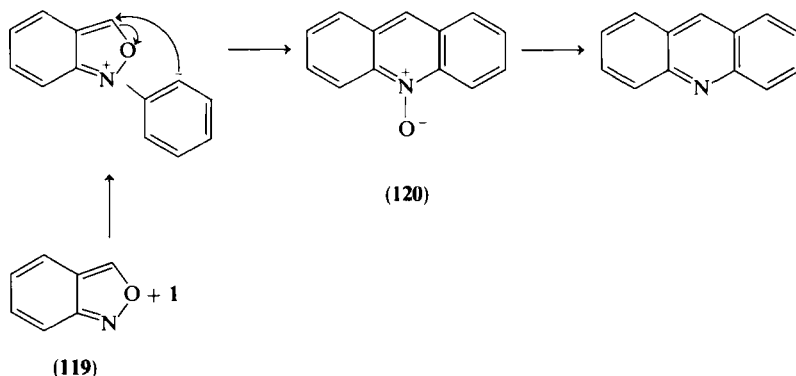


The compounds previously represented by structures **116** and **117** are now known to be the 2-(*o*-aminophenyl) benzotriazole derivatives **116a** and **117a**, respectively^{82a}; these revised structures are confirmed by an independent synthesis of **117a**. Their formation is rationalized by a 1,3-cycloaddition of benzyne to **9**, followed by rearrangement to give **118**, and successive N-phenylation, **118** → **116a** → **117a**.



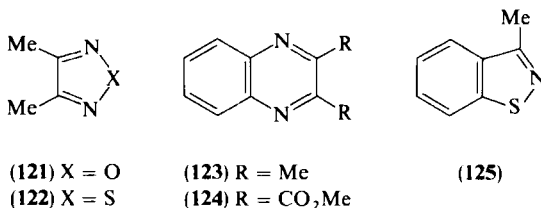
^{82a} P. G. Houghton and C. W. Rees, *J. Chem. Res. (S)* 303, (*M*) 3888 (1980).

Anthranil (**119**) and benzyne (from oxidation of **9** with lead tetraacetate) afford acridine (5%)⁸¹; depending on the sequence of bond forming and breaking, an oxygen-bridged cycloadduct and/or acridine *N*-oxide (**120**) may be intermediates in this reaction (Scheme 15), although **120** is known to react with benzyne in a different sense (Section IX). The addition of benzyne to oxazoles leads, ultimately, to anthracene derivatives in high overall yield.^{82b}



SCHEME 15

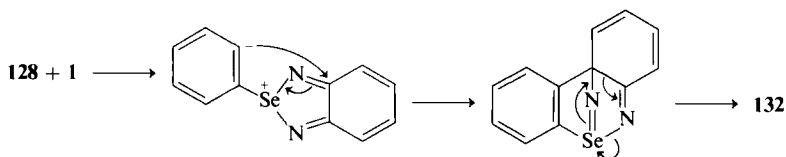
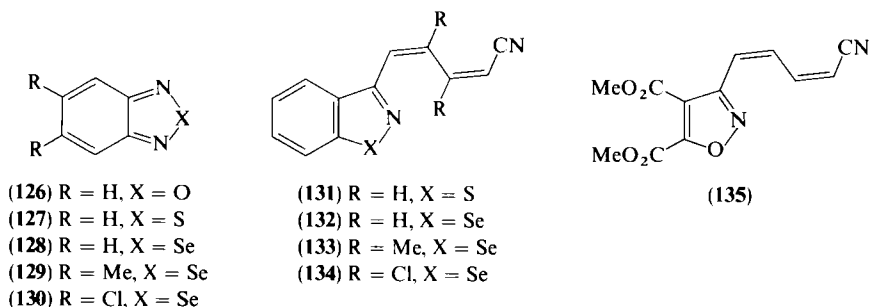
Reactions of a number of heterocycles containing the heterodiene system $\text{N}=\text{C}-\text{C}=\text{N}$ have been studied (see also Section VII). With very few exceptions, products arising from Diels–Alder additions are not observed; but some other reactions occur, as already exemplified by 2-methylbenzotriazole. The 1,2,5-oxadiazole **121** and 2,1,3-benzoxadiazole (**126**) are unreactive toward benzyne, which gave only biphenylene in high yield.⁸¹ However, four products obtained from benzyne and 3,4-dimethyl-1,2,5-thiadiazole (**122**) provide evidence for two competing cycloadditions to this ring system: the quinoxaline **123** and sulfur result from attachment of benzyne at both nitrogen atoms, and 3-methyl-1,2-benzisothiazole (**125**) (45%) and acetonitrile (53%) from attachment of benzyne at ring carbon and sulfur atoms.⁸³



^{82b} G. S. Reddy and M. V. Bhatt, *Tetrahedron Lett.* **21**, 3627 (1980).

⁸³ M. R. Bryce, P. Hanson, and J. M. Vernon, unpublished results.

2,1,3-Benzoselenadiazole (**128**) behaves as a heterodiene toward dimethyl acetylenedicarboxylate, with which it gives the quinoxaline **124** and selenium. But **128** reacts differently with benzyne (generated from **4** or from **9**) to give the 1,2-benzisoselenazole derivative **132** (88%) and a small amount of a cis,trans stereoisomer of **132**.⁸² The analogous adduct **131** is obtained in lower yield from benzyne and 2,1,3-benzothiadiazole (**127**). The structure of these benzyne adducts is strikingly reminiscent of **135**, which is obtained from a photochemical addition of dimethyl acetylenedicarboxylate to **126** via a nitrile oxide intermediate.⁸⁴ However, for reasons given elsewhere,⁸² a nitrile selenide is unlikely to be an intermediate in the formation of **132**, which is better explained by the mechanism outlined in Scheme 16. As in the case of thiophen (Section V,B), this is a 1,3-cycloaddition (in one or two steps) of benzyne to the heterocycle, enabled by the use of d orbitals on the sulfur or selenium atom.



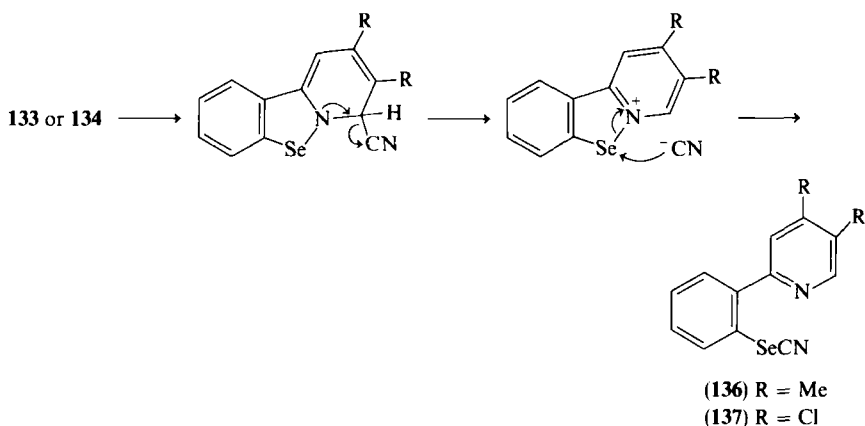
SCHEME 16

A series of adducts analogous to **132** has been prepared from benzyne and substituted 2,1,3-benzoselenadiazoles.^{84a} The adduct **133**, from 5,6-dimethyl-2,1,3-benzoselenadiazole (**129**), undergoes a further remarkable rearrangement either thermally or photochemically to give the selenocyanate **136**. The corresponding compound **137** is obtained directly from the reaction of benzyne with **130**, which implies that the adduct **134** is even more labile

⁸⁴ I. Yavari, S. Esfandiari, A. J. Mostashari, and P. W. W. Hunter, *J. Org. Chem.* **40**, 2880 (1975); W. Heinzelmann and P. Gilgen, *Helv. Chim. Acta* **59**, 2727 (1976).

^{84a} M. R. Bryce, C. D. Reynolds, P. Hanson, and J. M. Vernon, *J. C. S., Perkin I*, **607** (1981).

than **133**. A possible mechanism to account for this rearrangement is shown in Scheme 17.



SCHEME 17

B. MESOIONIC COMPOUNDS AND HETEROCYCLES WITHOUT A FORMAL DIENE SYSTEM

Recent developments in the chemistry of mesoionic compounds⁸⁵ include cycloaddition-elimination reactions, which afford novel synthetic routes to a variety of heterocyclic systems. These reactions may be seen as involving 1,3-dipolar cycloadditions, following Huisgen,⁸⁶ or alternatively as 1,4-cycloadditions to heterodiene systems,⁸⁷ depending on the choice of canonical structure to represent the mesoionic compound. Benzyne has been employed in such reactions less frequently than more stable acetylenic or ethylenic dipolarophiles.

The earliest example is the addition of benzyne (generated from **4** or by diazotization of anthranilic acid *in situ*) to *N*-phenyl sydnone (3-phenyl-1,2,3-oxadiazolium 5-oxide, **138**)⁸⁸; spontaneous loss of carbon dioxide from the intermediate adduct **139** gives 2-phenylindazole (**140**). Later workers have obtained **140** in higher yield (73%) and the corresponding 2,3-disubstituted indazoles from two other sydrones using benzyne generated by oxidation

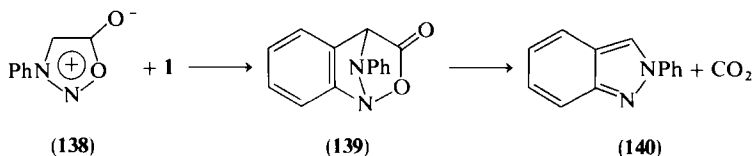
⁸⁵ For a recent review see W. D. Ollis and C. A. Ramsden, *Adv. Heterocycl. Chem.* **19**, 1 (1976).

⁸⁶ R. Huisgen, *Chem. Soc., Spec. Publ.* **21**, 51 (1967); R. Huisgen, H. Gotthardt, and R. Grashey, *Chem. Ber.* **101**, 536 (1968); H. Gotthardt and R. Huisgen, *ibid.*, 552; R. Huisgen and H. Gotthardt, *ibid.*, 1059; H. Gotthardt and R. Huisgen, *ibid.* **103**, 2611 (1970).

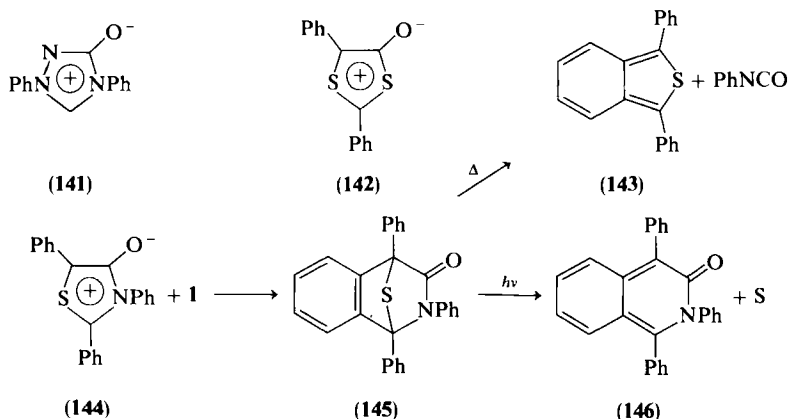
⁸⁷ Cf. K. T. Potts, E. Houghton, and U. P. Singh, *Chem. Commun.*, 1129 (1969); K. T. Potts and D. McKeough, *J. Am. Chem. Soc.* **95**, 2750 (1973).

⁸⁸ A. Ya. Lazaris, *Zh. Org. Khim.* **2**, 1322 (1966) [*CA* **66**, 65426 (1967)]; H. Gotthardt, R. Huisgen, and R. Knorr, *Chem. Ber.* **101**, 1056 (1968).

of **9**.⁸⁹ The same method of benzyne generation achieves no reaction with 1,4-diphenyl-1,2,4-triazolium 3-oxide (**141**), but at a higher temperature benzyne generated from **7** reacts with **141** to give **140** (34%).⁸⁹



The primary cycloadduct **145** from the mesoionic 1,3-thiazol-5-one (**144**) and benzyne (generated from **9**) was isolated in 78% yield. Thermal decomposition of **145** (in boiling xylene) gave 1,3-diphenylbenzo[*c*]thiophen (**143**) and phenyl isocyanate, but in striking contrast UV irradiation of **145** yielded 1,2,4-triphenylisoquinolin-3-one (**146**) by extrusion of sulfur.⁸⁹ The 1:1 adducts corresponding to **145** from 1,3-thiazolium 4-oxides and dimethyl acetylenedicarboxylate or dibenzoylacetylene are not isolable, but they fragment under the reaction conditions to either pyridin-2-one or thiophen derivatives, depending on the pattern of substitution in the mesoionic compound.^{87,90} The mesoionic 1,3-dithiol-4-one **142** and benzyne (from oxidation of **9**) also afforded **143** (36%) by a similar cycloaddition and loss of carbonyl sulfide.⁸⁹

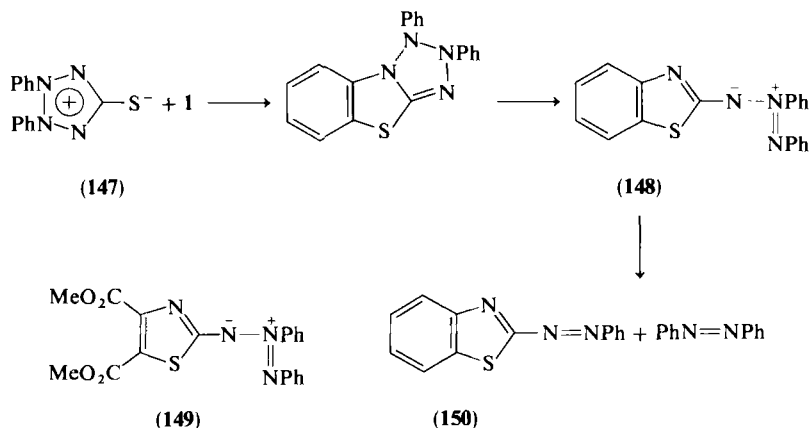


2-Phenylazo-1,3-benzothiazole (**150**) (11%) and azobenzene (9%) were the products obtained from the reaction of 2,3-diphenyltetrazolium 5-sulfide

⁸⁹ S. Nakazawa, T. Kiyosawa, K. Hirakawa, and H. Kato, *J. C. S., Chem. Commun.*, 621 (1974).

⁹⁰ K. T. Potts, E. Houghton, and U. P. Singh, *J. Org. Chem.* **39**, 3627 (1974); cf. K. T. Potts, J. Baum, E. Houghton, D. N. Roy, and U. P. Singh, *ibid.*, 3619.

(dehydrodithizone, **147**) and benzyne (from anthranilic acid).⁹¹ These azo compounds are considered to be formed by loss and/or dimerization of aryl nitrenes from a rearranged adduct **148**. Dimethyl acetylenedicarboxylate and **147** give the analogous adduct **149**, the structure of which was established by X-ray diffraction.⁹¹ However, decomposition of **149** was not observed.



1,2-Dithiole-3-thiones (e.g. **151**) are not mesoionic according to the usual definition,⁸⁵ although the ring system becomes aromatic if charge separation is allowed. The addition of benzyne to **151** (Ar = Ph) has been reported by two research groups using various methods for benzyne generation^{92,93}; the highest yield (55%) of a 1:1 adduct, 2-thiophenacylidene-1,3-benzodithiole (**152**; Ar = Ph), was obtained using **9** as the benzyne precursor. Formation of **152** may occur in a single step as shown, or via cycloaddition of benzyne to the 1,3-dipolar $\text{S}=\text{C}=\text{S}$ system preceding opening of the dithiole ring. Adducts analogous to **152** have been obtained from other 1,2-dithiole-3-thiones (**154–156**)⁹³ although the 4-phenyl derivative (**157**) and benzyne afforded the aldehyde **158** instead of the expected thioaldehyde, probably because of oxidation by lead tetraacetate (for generation of benzyne from **9**).⁹² A comparison of the reactions of **151** with arylacetylenes and with dimethyl acetylenedicarboxylate is again informative⁹⁴: 1:1 adducts corresponding

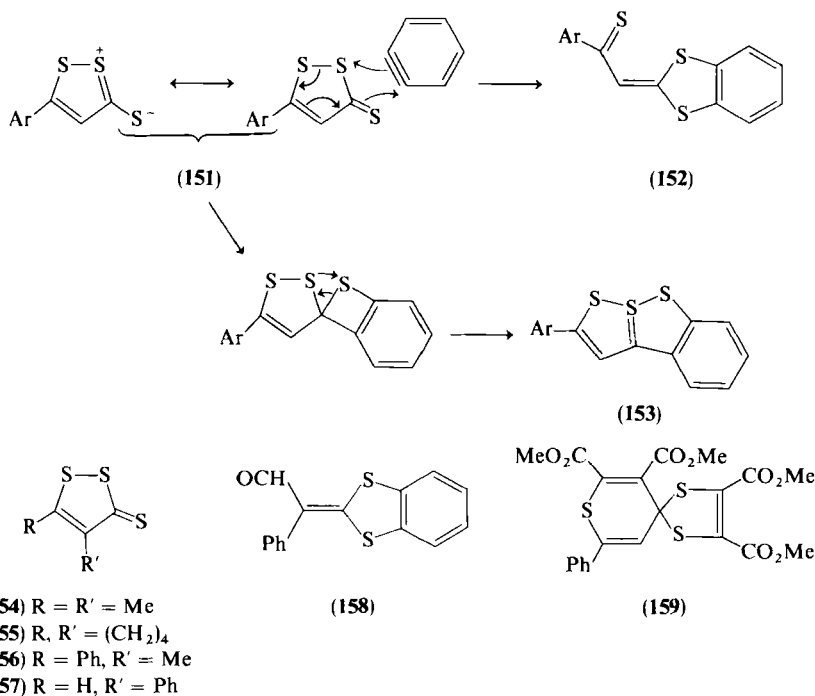
⁹¹ G. V. Boyd, T. Norris, P. F. Lindley, and M. M. Mahmoud, *J. C. S., Perkin I*, 1612 (1977).

⁹² D. B. J. Easton and D. Leaver, *Chem. Commun.*, 585 (1965); D. B. J. Easton, D. Leaver, and T. J. Rawlings, *J. C. S., Perkin I*, 41 (1972).

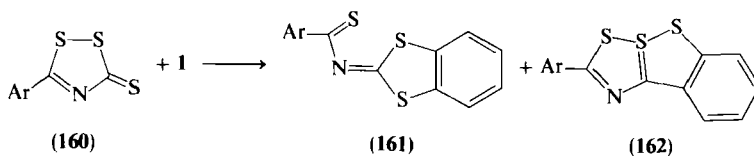
⁹³ J.-M. Decrouen, D. Pacquer, and R. Pou, *C. R. Acad. Sci., Ser. C* **279**, 259 (1974); D. Pacquer and R. Pou, *Bull. Soc. Chim. Fr.*, 120 (1976).

⁹⁴ H. Behringer, D. Bender, J. Falkenberg, and R. Wiedenmann, *Chem. Ber.* **101**, 1428 (1968); H. Davy, M. Demuyne, D. Pacquer, A. Rouessac, and J. Vialle, *Bull. Soc. Chim. Fr.*, 2057 (1968).

to **152** are obtained, but with the acetylene ester 1:2 adducts with the interesting spiro structure **159** have also been characterized.⁹²

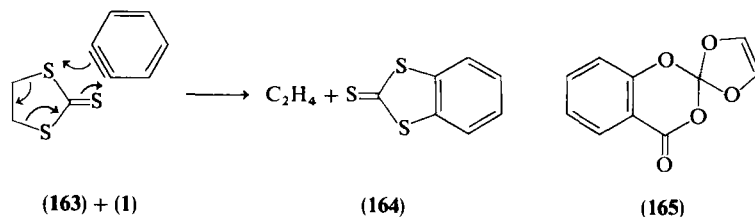


Pacquer *et al.* also recognized a second series of intensely colored 1:1 adducts, the trithiapentalenes **153**, from benzyne and 5-aryl-1,2-dithiole-3-thiones (**151**).⁹³ Although very little of **153** ($\text{Ar} = \text{Ph}$) was obtained ($\leq 1\%$), *p*-anisyl, *p*-tolyl, and *p*-chlorophenyl compounds were formed in higher yields. Unsuccessful attempts to achieve the conversion **152** \rightarrow **153** render more likely an independent pathway for the formation of **153**, e.g., one involving an initial 1,2-cycloaddition of benzyne to the exocyclic $\text{C}=\text{S}$ bond of **151**. Derivatives of the related 1,2,4-dithiazole-3-thione system **160** and benzyne also afford two series of 1:1 adducts **161** and **162** corresponding to **152** and **153**, respectively.⁹³



Benzyne (generated from **7** or from **9**) also reacted with 1,3-dithiolan-2-thione (**163**) to give 1,3-benzodithiole-2-thione (**164**) (9–13%).⁹² Evidence for

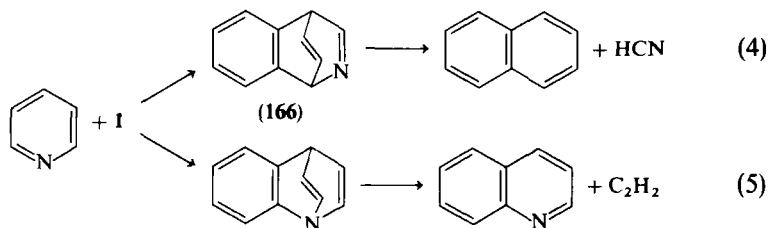
a concerted cycloaddition-elimination mechanism in this case is obtained from a study of the analogous reaction of derivatives of **163** with dimethyl acetylenedicarboxylate. This result contrasts with that obtained from the decomposition of **4** in vinylene carbonate⁹⁵; one product (2%), tentatively assigned the spiro structure **165**, incorporates the benzyne precursor **5** rather than benzyne itself.



VII. Six-Membered Ring Systems

A. AZINES

The reaction of benzyne with pyridine has been studied only at 690°C (benzyne generated from phthalic anhydride).⁹⁶ The main condensable products in order of decreasing abundance were naphthalene, phenylpyridines (three isomers), bipyridyls, and quinoline. It is necessary to consider two modes of 1,4-cycloaddition, followed by rearomatization, to account for the formation of naphthalene (Eq. 4) and quinoline (Eq. 5), respectively.



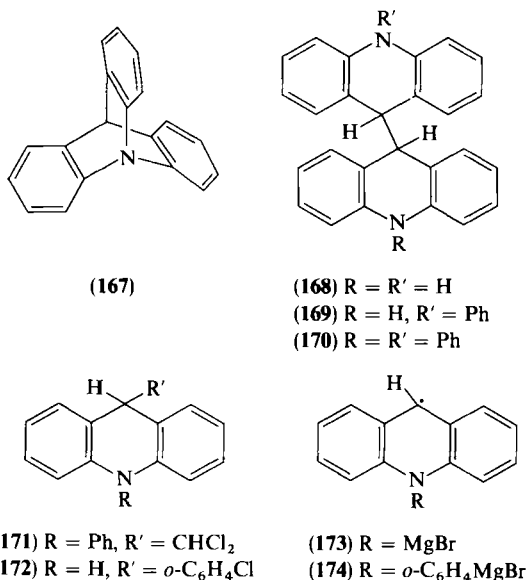
The latter pathway is relatively disfavored, as the requisite diene system includes a terminal nitrogen atom. The enthalpy term for the rearomatization of the intermediate adduct (166) will favor extrusion of hydrogen cyanide rather than acetylene, so that isoquinoline is formed in only trace amounts, if at all. Fields and Meyerson also consider mechanisms involving 1,2-cycloaddition of benzyne to pyridine to account for formation of the same

⁹⁵ J. M. Rao and S. Mallikarjuna, *Tetrahedron Lett.*, 283 (1979).

⁹⁶ E. K. Fields and S. Meyerson, *J. Org. Chem.* **31**, 3307 (1966).

products,^{58,96} but there is no evidence that requires them to be involved. Similar products were obtained, but in lower overall yields, from pyridine and tetrachloro- or tetraphenylbenzyne (generated by pyrolysis of the corresponding X_4 -phthalic anhydride).⁹⁶

In spite of the ready formation of triptycene from anthracene and benzyne, the azatriptycene **167** cannot be obtained directly from acridine and benzyne. Instead, only biphenylene (**17**) was obtained (benzyne generated from **9**),⁸¹ or 2-fluorobiphenyl (using *o*-fluorophenyllithium), or the products were 4-phenylacridine (2%), *N*-phenylacridone (4%), and biacridyl derivatives **168**–**170** (together 50%), (benzyne generated from *o*-FC₆H₄MgBr),⁹⁷ or **171** (benzyne generated from **4** in dichloromethane).⁹⁸ The formation of **168** does not involve benzyne at all but reductive dimerization of acridine via radicals **173**; hence formation of **169** and **170** was attributed to free radical



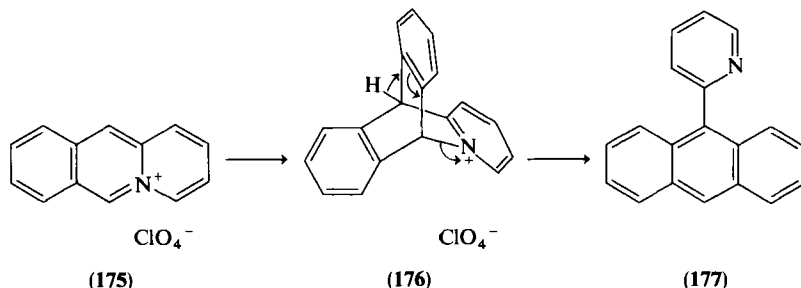
reactions involving **174**. An alternative possibility, the successive *N*-phenylation **168** → **169** → **170** by attack of benzyne, was not considered. *N*-Phenylacridone is apparently formed by autoxidative cleavage of **169**. An indirect synthesis of **167** was achieved via intramolecular *N*-arylation of an aryne intermediate when the acridan derivative **172** was treated with potassium amide in liquid ammonia.⁹⁹

⁹⁷ G. Wittig and K. Niethammer, *Chem. Ber.* **93**, 944 (1960).

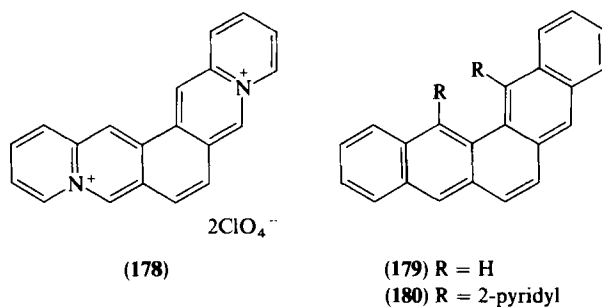
⁹⁸ B. H. Klanderman, *Tetrahedron Lett.*, 4639 (1966).

⁹⁹ G. Wittig and G. Steinhoff, *Justus Liebigs Ann. Chem.* **676**, 21 (1964).

Phenazine is similarly unreactive toward benzyne (by oxidation of **9**), which gave only biphenylene and small amounts of unidentified highly colored products.⁸¹ On the other hand, the benzo[*b*]quinolizinium salt **175** reacts like anthracene with benzyne (generated by aprotic diazotization of anthranilic acid in refluxing acetonitrile) to give the Diels–Alder adduct **176** (78%).¹⁰⁰ Aromatization of **176** to 9-(2-pyridyl)anthracene (**177**) is accomplished in refluxing acetic anhydride in the presence of sodium acetate.



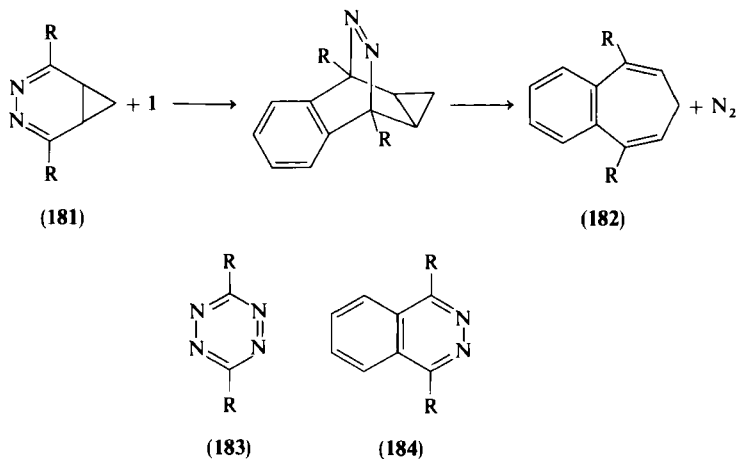
Alternatively, reduction of **176** with sodium borohydride (probably to a dihydropyridine, although this intermediate was not characterized) followed by thermolysis in acetic acid or acetic anhydride affords anthracene (93%) and pyridine or dihydropyridines. These reaction sequences have been employed for the synthesis of overcrowded anthracene derivatives containing substituents with unfavorable *peri* interactions¹⁰⁰; of particular interest is the conversion of **178** via its 1:2 adduct with benzyne into the pentaphenes **179** and **180**.



Although the heterodiene system $\text{N}=\text{C}-\text{C}=\text{N}$ is usually unreactive toward the addition of benzyne (see also Section VI,A), compounds containing the system $\text{C}=\text{N}-\text{N}=\text{C}$ will react with benzyne in a 1,4-cycloaddition, which is followed by extrusion of the azo bridge as nitrogen. This pattern of

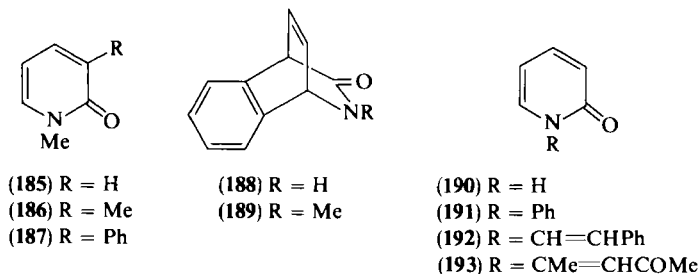
¹⁰⁰ D. L. Fields, T. H. Regan, and R. E. Graves, *J. Org. Chem.* **36**, 2995 (1971); D. L. Fields, *ibid.*, 3002; cf. H. Hart, J. B.-C. Jiang, and R. K. Gupta, *Tetrahedron Lett.*, 4639 (1975).

reaction occurs for 4,5-dihydro-1,2-diazines **181** ($R = \text{Ph}$, $p\text{-C}_6\text{H}_4\text{CF}_3$, CO_2Me), as well as for 1,2,4,5-tetrazines **183** ($R = \text{Ph}$, CO_2Me), with benzyne (generated from **4**) to give the products **182** and **184**, respectively.¹⁰¹ An unidentified 1:1 adduct from benzyne and **181** ($R = \text{Ph}$) was also obtained (5%).



B. HYDROXY DERIVATIVES OF AZINES

1-Methyl-2H-pyridin-2-one (**185**) and benzyne (generated by diazotization of anthranilic acid) afforded the Diels–Alder adduct, **189** (10%).¹⁰² Under similar conditions, 1,x-dimethylpyridin-2-ones (including **186**) and 1-styrylpyridin-2-one (**192**) gave the corresponding 1,4-cycloadducts (4–13% and 40%, respectively), but two other *N*-vinyl derivatives (including **193**)

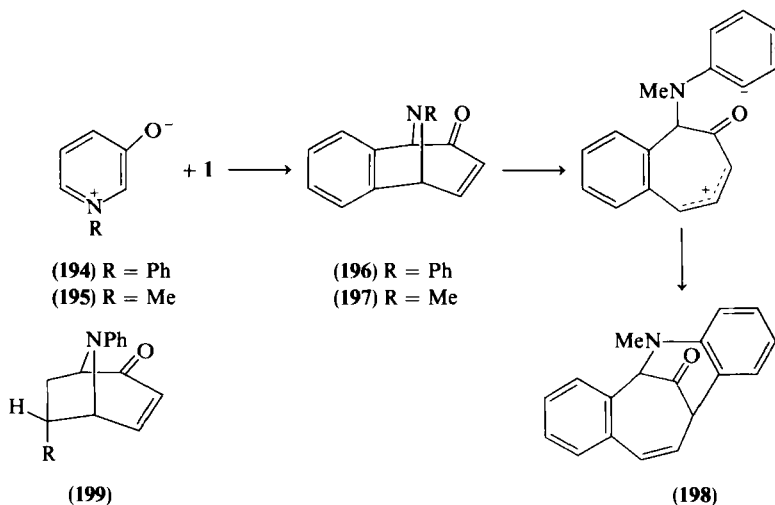


¹⁰¹ R. E. Moerck and M. A. Battiste, *J. C. S., Chem. Commun.*, 1171 (1972); J. Sauer and G. Heinrichs, *Tetrahedron Lett.*, 6141 (1966).

¹⁰² L. Bauer, C. L. Bell, and G. E. Wright, *J. Heterocycl. Chem.* **3**, 393 (1966); E. B. Sheinin, G. E. Wright, C. L. Bell, and L. Bauer, *ibid.* **5**, 859 (1968); P. S. Mariano, P. L. Huesmann, R. L. Beamer, and D. Dunaway-Mariano, *Tetrahedron* **34**, 2617 (1978).

afforded a product which was inconclusively identified as **188**. Use of an alternative source of benzyne (from chlorobenzene and sodium amide) caused the reaction with **185** to take a different course, giving the 3-phenyl derivative **187** (5%) instead.¹⁰² The unsubstituted 2*H*-pyridin-2-one (**190**) and benzyne gave a mixture of the *N*-phenyl derivative **191** (2%), 2-phenoxy pyridine (4%), and acridone (which is formed via a reaction of benzyne with anthranilic acid).

Katritzky and co-workers have demonstrated the 1,3-dipolar character of 3-oxidopyridinium betaines by cycloaddition of olefinic and acetylenic dipolarophiles, including in some cases benzyne, across the 2- and 6-positions of the pyridine ring. Thus, 1-phenylpyridinium 3-oxide (**194**) and benzyne afford the 1:1 adduct **196** (35%); 1-methylpyridinium 3-oxide (**195**) and benzyne give a 1:2 adduct (21%), which is formulated as **198** and its formation explained in terms of the mechanism outlined in Scheme 18 (cf. Scheme 12).¹⁰³ Attempts to substantiate this mechanism were unsuccessful, since compounds **199** (R = CN, CO₂Me) analogous to the intermediate 1:1 adduct **197** failed to react with benzyne under similar conditions. 1,6-Dimethylpyridinium 3-oxide with benzyne gave a 1:2 adduct of the same type as **198**.¹⁰³

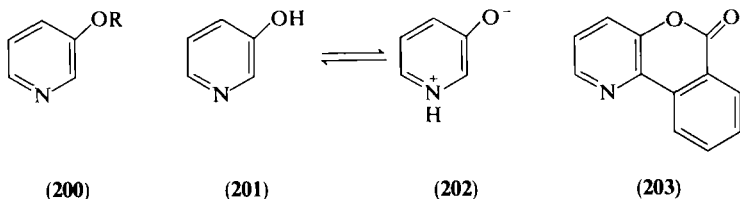


SCHEME 18

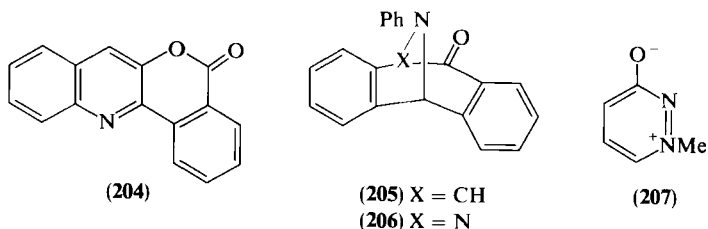
3-Pyridyl esters **200** (R = COMe, COPh, COCF₃) and nitrophenyl ethers react with benzyne to give **196**.¹⁰³ [The ether **200** (R = 2,4-dinitrophenyl) was for some time mistakenly believed to be the betaine, 1-(2,4-dinitrophenyl)-pyridinium 3-oxide, and its reaction with benzyne was at first ascribed to the

¹⁰³ N. Dennis, A. R. Katritzky, T. Matsuo, S. K. Parton, and Y. Takeuchi, *J. C. S., Perkin I*, 746 (1974); N. Dennis, A. R. Katritzky, and S. K. Parton, *ibid.*, 2285 (1976).

latter compound.¹⁰⁴] The formation of **196** in these cases is understood in terms of the following mechanism: N-phenylation of **200** by benzyne forms a pyridinium ester or ether, which undergoes hydrolysis or alcoholysis to **194** under the conditions of benzyne generation from anthranilic acid and pentyl nitrite in refluxing 1,2-dichloroethane and diglyme; finally **194** forms **196** by further reaction with benzyne.



3-Hydroxypyridine (**201**) itself possesses latent 1,3-dipolar character because of tautomerism involving 1-protiopyridinium 3-oxide (**202**). Aprotic diazotization of anthranilic acid in the presence of **201** gives two heterocyclic products [**196** (20%) and **203** (23%)] which were isolated in separate experiments run under almost identical conditions.^{103,105} Formation of the bis-adduct **196** must involve cycloaddition of benzyne to **202** and N-phenylation and there is some evidence from related additions to 2*H*-phthalazin-1-one (**208**) that the steps occur in this order.^{37b} Formation of the isocoumarin structure **203** apparently involves electrophilic substitution of **201** by the benzyne precursor **5**, followed by lactonization. From 3-hydroxy-6-methylpyridine compounds analogous to **196** and **203** were also obtained (10 and 29%, respectively). 3-Hydroxyquinoline afforded only the corresponding isocoumarin **204** (20%) whereas 4-hydroxyisoquinoline gave 4-phenoxyisoquinoline (12%) and the bis-adduct **205** (12%) with benzyne.^{103,105}

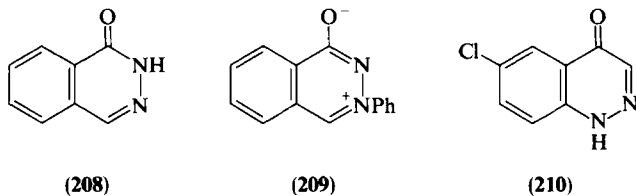


The behavior of some related hydroxydiazine derivatives has also been examined. Whereas the pyridazinium betaine **207** is unreactive toward

¹⁰⁴ N. Dennis, A. R. Katritzky, S. K. Parton, and Y. Takeuchi, *J. C. S., Chem. Commun.*, 707 (1972); N. Dennis, B. Ibrahim, A. R. Katritzky, and Y. Takeuchi, *ibid.*, 292 (1973); N. Dennis, B. Ibrahim, A. R. Katritzky, G. Taulov, and Y. Takeuchi, *J. C. S., Perkin I*, 1883 (1974).

¹⁰⁵ N. Dennis, A. R. Katritzky, and S. K. Parton, *J. C. S., Chem. Commun.*, 1237 (1972); *J. C. S., Perkin I*, 750 (1974).

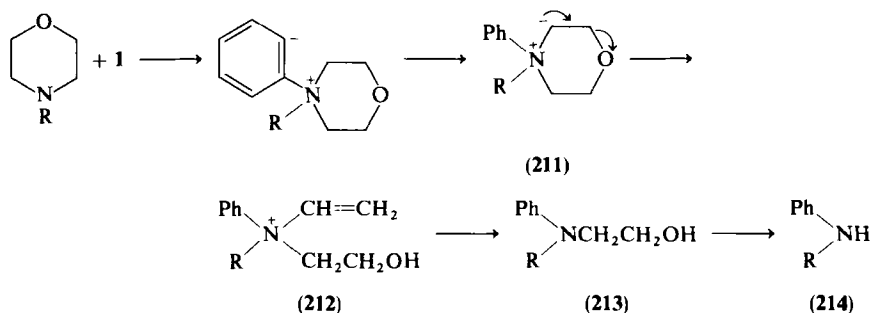
dipolarophiles, 2*H*-phthalazin-1-one (**208**) and benzyne (from *o*-carboxybenzenediazonium chloride) afforded the 1:2 adduct **206** in high yield.^{37b} The phthalazinium betaine **209**, however, failed to react with benzyne under similar conditions, so that it is probably not an intermediate in the reaction of **208** → **206**. The 1*H*-cinnolin-4-one **210** reacts like **208** with benzyne, although the corresponding 1:2 adduct was obtained as a red gum and characterized as the 2,4-dinitrophenylhydrazone derivative.^{37b}



C. REDUCED AZINES

Piperidine or lithium piperidide and benzyne form *N*-phenylpiperidine, as expected,^{39,106,107} but the same product (40–50%) was also obtained unexpectedly from *N*-methylpiperidine, fluorobenzene, and phenyllithium before the formation of benzyne under these conditions was properly recognized.²¹

A series of *N*-alkylmorpholines gives secondary and tertiary aniline derivatives **213** and **214** when treated with bromobenzene and sodium amide.¹⁰⁸ A route for formation of these products via the ylid **211** is outlined in Scheme 19, in which the formation of **211** is similar to that of **16** in Scheme 2 and the step **212** → **213** is similar to the decomposition of **33** in Scheme 5. The final



SCHEME 19

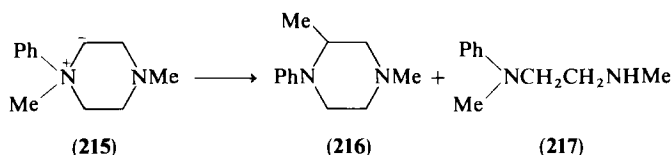
¹⁰⁶ C. H. Horning and F. W. Bergstrom, *J. Am. Chem. Soc.* **67**, 2110 (1945).

¹⁰⁷ R. Huisgen and J. Sauer, *Chem. Ber.* **91**, 1453 (1958); R. Huisgen, W. Mack, and L. Möbius, *Tetrahedron* **9**, 29 (1960).

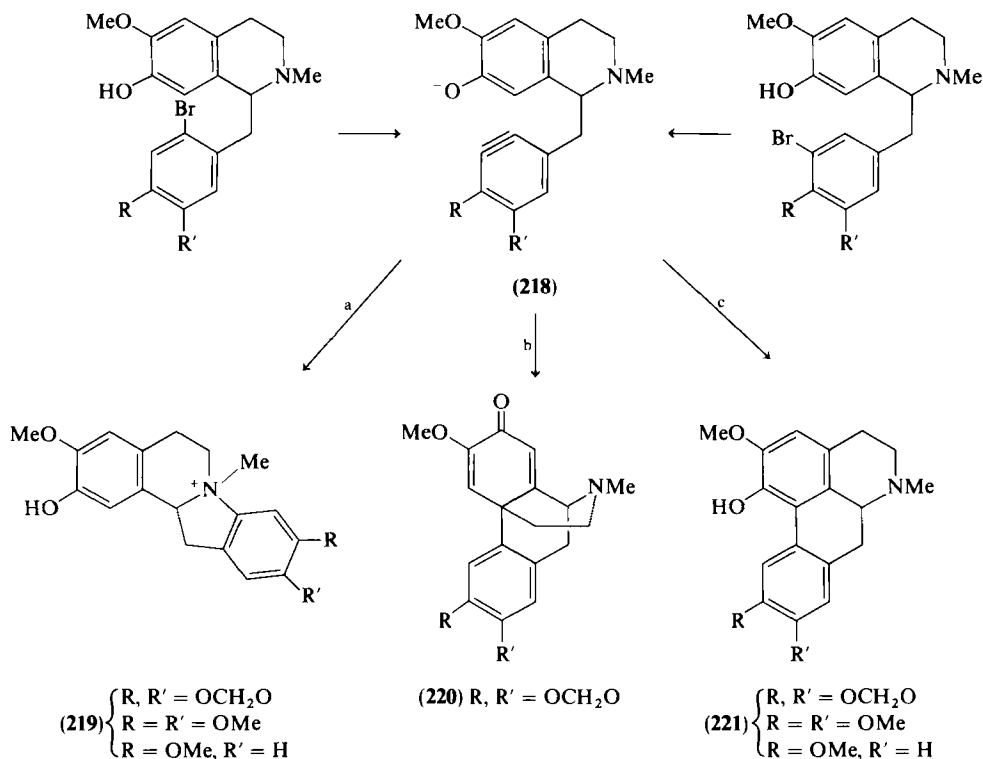
¹⁰⁸ T. Kametani, K. Kigasawa, H. Hiiragi, and T. Aoyama, *J. Org. Chem.* **37**, 1450 (1972).

dealkylation step **213** \rightarrow **214** ($R = \text{Me}$) was accomplished independently in low yield by heating with sodium amide in *N*-methylmorpholine. Treatment of *o*-chloroanisole or *o*-benzyloxychlorobenzene with sodium amide in the presence of *N*-methylmorpholine gives *m*-alkoxyanilines corresponding to **213** and **214** ($R = \text{Me}$) via cine-substitution of aryne intermediates.¹⁰⁸

N,N'-Dimethylpiperazine reacts similarly with benzyne (from bromobenzene and sodium amide) to give *N*-methylaniline (**214**; $R = \text{Me}$), **217** (corresponding to **213**; $R = \text{Me}$), and a third product **216** which is formed via Stevens rearrangement of the ylid **215**.¹⁰⁸

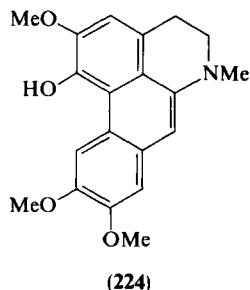
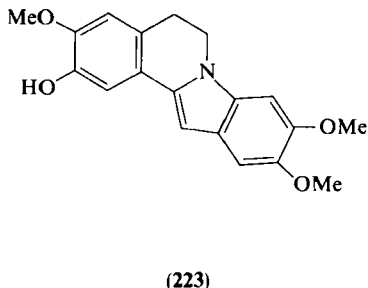
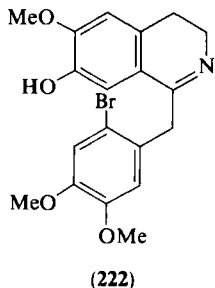


Intramolecular additions to aryne intermediates **218** from 1-(2-bromobenzyl)- or 1-(3-bromobenzyl)-1,2,3,4-tetrahydroisoquinoline derivatives are the basis for some elegant syntheses of natural product structures. In Scheme 20,



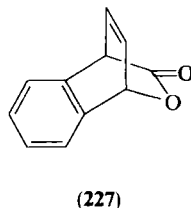
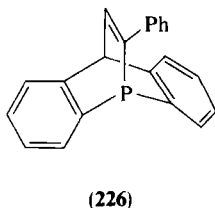
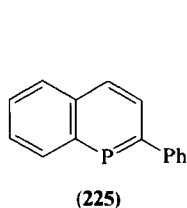
SCHEME 20

paths a, b, and c define cyclizations through 2-, 4a-, and 8-positions of the isoquinoline moiety, leading to dibenzoindolizines **219**, morphinandienones **220**, and aporphines **221**, respectively.^{109,110} Two of these cyclizations have also been achieved in single stage reactions from 3,4-dihydroisoquinoline derivatives, (e.g., **222** → **223**, and the preparation of **224** from the methiodide of **222** by treatment with sodium methanesulfonylmethanide).¹¹¹



D. RINGS CONTAINING HETEROATOMS OTHER THAN NITROGEN

1,4-Cycloaddition of benzyne (from *o*-FC₆H₄MgBr) with 2-phenyl-1-phosphanaphthalene (**225**) gives the novel structure **226** (17%), containing phosphorus at a bridgehead position; some acetylenes react similarly with **225**.¹¹² An adduct of the same type (**24**; containing R = As at a bridgehead position), obtained (33%) from arsabenzene and benzyne (generated from **4**), was subsequently converted to the unstable 1-arsanaphthalene.¹¹³ 1,4-Cycloaddition of benzyne also occurs with 2-pyrone, but loss of carbon dioxide from the primary adduct **227** follows spontaneously to give naphthalene.¹⁵



¹⁰⁹ S. V. Kessar, S. Batra, and S. S. Gandhi, *Indian J. Chem.* **8**, 468 (1970); S. V. Kessar, R. Randhawa, and S. S. Gandhi, *Tetrahedron Lett.*, 2923 (1973).

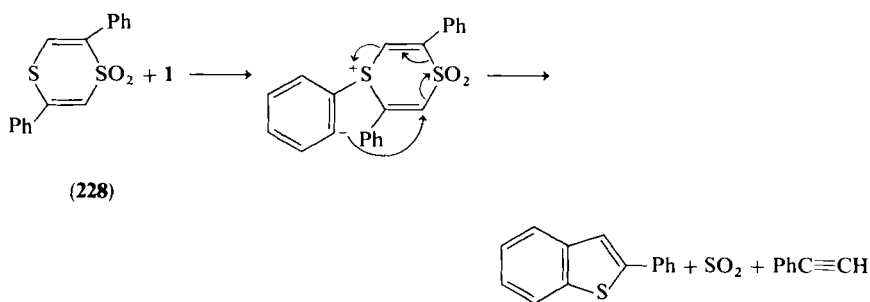
¹¹⁰ T. Kametani and K. Ogasawara, *J. Chem. Soc. C*, 2208 (1967); T. Kametani, S. Shibuya, K. Kigasawa, M. Hiiragi, and O. Kusama, *ibid.*, 2712 (1971); T. Kametani, K. Fukumoto, and T. Nakano, *J. Heterocycl. Chem.* **9**, 1363 (1972); T. Kametani, A. Ujiie, K. Takahashi, T. Nakano, T. Susuki, and K. Fukumoto, *Chem. Pharm. Bull.* **21**, 766 (1973).

¹¹¹ T. Kametani, S. Shibuya, and S. Kano, *J. C. S., Perkin I*, 1212 (1973).

¹¹² G. Märkl and K. H. Heier, *Tetrahedron Lett.*, 4369 (1974).

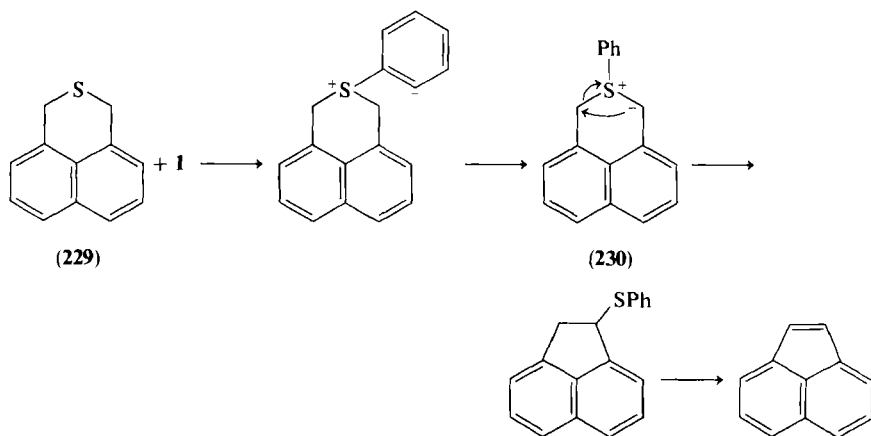
¹¹³ A. J. Ashe, D. J. Bellville, and H. S. Friedman, *J. C. S., Chem. Commun.*, 880 (1979).

The reaction of benzyne (from anthranilic acid) with 2,5-diphenyl-1,4-dithiin 1,1-dioxide (**228**) follows the course outlined in Scheme 21 to give 2-phenylbenzo[*b*]thiophen (27%), phenylacetylene, and sulfur dioxide.¹¹⁴ Instead of the 1,5-addition shown, it is possible to envisage the formation of a 1,3-cycloadduct as intermediate analogous to that drawn for addition to thiophen (Scheme 9), although no such intermediate was detected. Compound **228** reacts in the same manner with dimethyl acetylenedicarboxylate.¹¹⁴



SCHEME 21

Reaction of the naphthothiin **229** with benzyne produces acenaphthylene in high yield via formation and Stevens rearrangement of the sulfur ylid **230** (Scheme 22).¹¹⁵



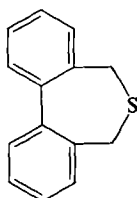
SCHEME 22

¹¹⁴ K. Kobayashi and K. Mutai, *Tetrahedron Lett.*, 905 (1978).

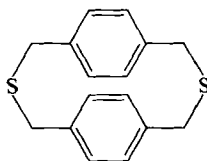
¹¹⁵ R. H. Mitchell, unpublished results.

VIII. Seven-Membered and Larger Ring Systems

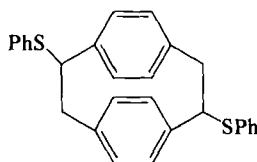
The dibenzodihydrothiepin **231** reacts in the same way as **229** with benzyne to give phenanthrene in high yield.¹¹⁵ The same pattern of reaction has been used to extrude sulfur atoms, usually two at a time, from larger rings (e.g., **232**) for the synthesis of cyclophanes.¹¹⁶ However, in such cases elimination of thiophenol does not follow spontaneously after the Stevens rearrangement, and indirect methods for subsequent removal of the SPh groups (e.g., from **233**) are necessary.



(231)



(232)



(233)

Surprisingly, no reactions of benzyne with azepines or other seven-membered heterocycles have yet been reported.

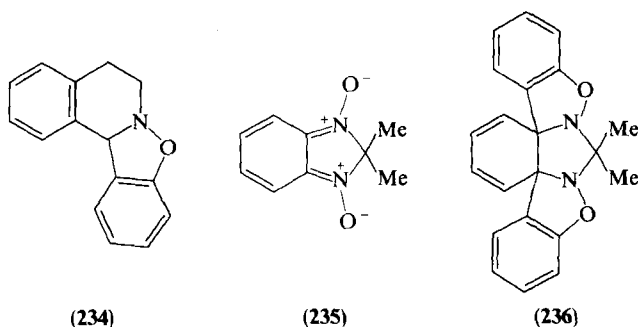
IX. Heterocyclic *N*-Oxides

The chemistry of heterocyclic *N*-oxides prior to 1970 has been the subject of an extensive review,¹¹⁷ but most of their reactions with benzyne have been studied more recently. In *N*-oxides the disposition of bonds at the nitrogen atom can be linear (nitrile oxides), trigonal (nitrones), or tetrahedral (tertiary amine oxides). The nitrile oxide group $\text{—C}\equiv\text{N}^+\text{—}\bar{\text{O}}$ cannot be part of a heterocyclic system, but it characteristically reacts with benzyne in a 1,3-cycloaddition to give 1,2-benzisoxazoles (e.g., **19** \rightarrow **20**).²⁷ Nitrones, which contain the group $\text{C}=\text{N}^+\text{—}\bar{\text{O}}$, are the most important class of heterocyclic *N*-oxides, and they are likewise reactive as 1,3-dipoles. If the $\text{C}=\text{N}$ bond is not part of an aromatic system, then a 1,3-cycloadduct with benzyne is usually isolable. Thus, **234** is obtained from 3,4-dihydroisoquinoline 2-oxide,²⁸ and the 2*H*-benzimidazole 1,3-dioxide **235** gives the interesting bis-adduct **236**

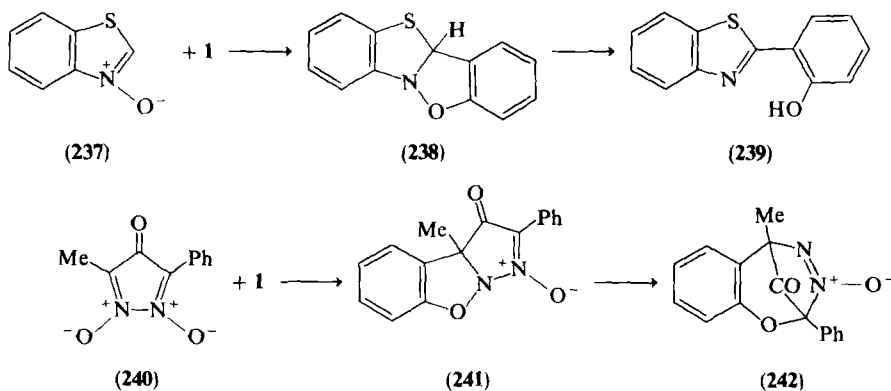
¹¹⁶ T. Otsubo and V. Boekelheide, *Tetrahedron Lett.*, 3881 (1975); *J. Org. Chem.* **42**, 1085 (1977); R. H. Mitchell, *Heterocycles* **11**, 563 (1978).

¹¹⁷ A. R. Katritzky and J. M. Lagowski, "Chemistry of the Heterocyclic *N*-Oxides." Academic Press, New York, 1971.

(37%), by reaction of benzyne with the nitron groups in preference to either cyclodiene moiety.¹¹⁸



Benzofuroxan, the *N*-oxide of **126**, does not react with benzyne (generated by oxidation of **9**), which gave only biphenylene (**17**).⁸¹ In most other cases benzyne reacts with the *N*-oxides of azoles and azines to give rearranged adducts; two particular rearrangement pathways are most commonly observed for the primary 1,3-cycloadducts. Rearomatization to an *o*-hydroxyphenyl derivative of the starting azole or azine system may occur (e.g., **237** → **238** → **239**).¹¹⁹ Alternatively, a sigmatropic shift moves the phenoxy group from nitrogen to a carbon atom (e.g., **240** → **241** → **242**).¹²⁰



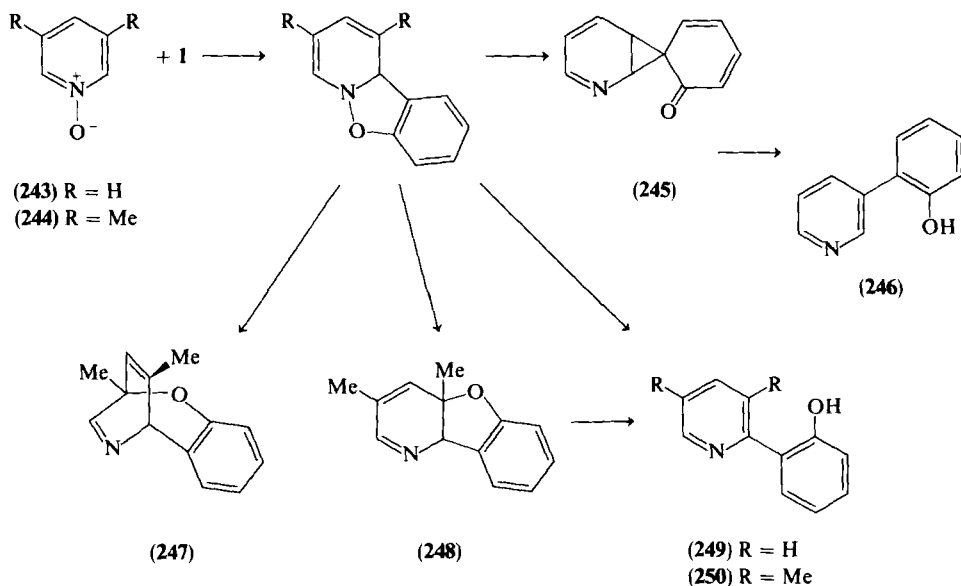
The reaction of pyridine 1-oxide (**243**) with benzyne has been studied under various conditions; the highest yield (53%) of the major product, 3-*o*-hydroxyphenylpyridine (**246**), was obtained when benzyne was generated by oxidation

¹¹⁸ D. W. S. Latham, O. Meth-Cohn, H. Suschitzky, and J. A. L. Herbert, *J. C. S., Perkin I*, 470 (1977).

¹¹⁹ S. Takahashi, S. Hashimoto, and H. Kano, *Chem. Pharm. Bull.* **18**, 1176 (1970).

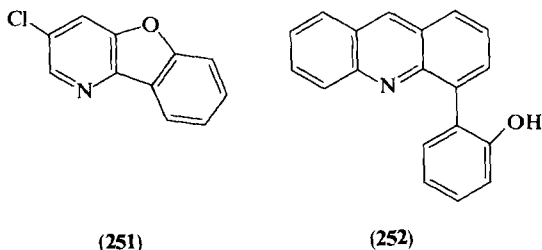
¹²⁰ J. P. Freeman and R. C. Grabiak, *J. Org. Chem.* **41**, 2531 (1976); cf. J. P. Freeman, J. A. Kassner, and R. C. Grabiak, *ibid.* **40**, 3402 (1975).

of **9** with 1-chlorobenzotriazole, and the isomeric adduct **249** (6%) was also obtained.¹²¹ The formation of **246**, but not of **249**, was considered to involve the spiro intermediate **245** (Scheme 23). *o*-Hydroxyphenylpyridines corresponding to **246** were also obtained from cyano- and methylpyridine 1-oxides.



SCHEME 23

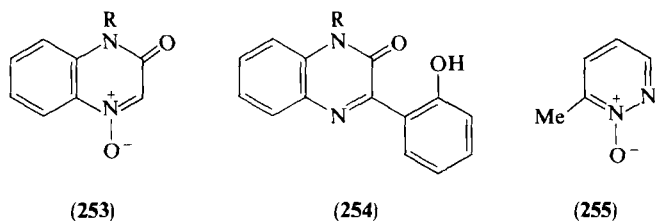
However, 3,5-dimethylpyridine 1-oxide (**244**) and benzyne (from decomposition of **4** below 45°C) afforded **250** (24%) and isomeric adducts **247** and **248** (25 and 23%, respectively) via 1,3- and 1,5-sigmatropic rearrangement of the primary 1,3-cycloadduct (Scheme 23).¹²¹ Both **247** and **248** also rearranged at 100°C to form **250**. The rearranged adduct corresponding to **248** from 3,5-dichloropyridine 1-oxide spontaneously lost hydrogen chloride at 0°C to give 3-chloropyrido[3,2-*b*]benzofuran (**251**).¹²¹ Acridine *N*-oxide (**120**)



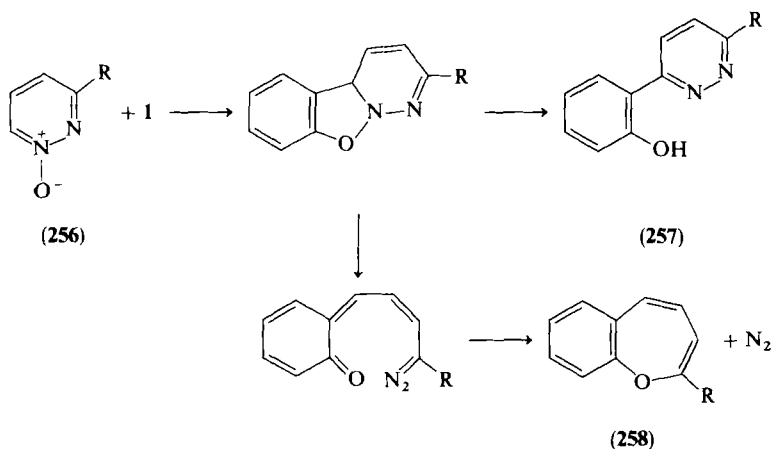
¹²¹ R. A. Abramovitch and I. Shinkai, *J. Am. Chem. Soc.* **96**, 5265 (1974).

and benzyne (from decomposition of **8**) afford 4-*o*-hydroxyphenylacridine (**252**) (25%).⁹⁹

Similar reactions are found for *N*-oxides in the diazine series. Thus, 4*H*-quinoxalin-3-one 1-oxides **253** (R = H, Me) and benzyne give the hydroxyphenyl derivatives **254** (95%).¹²² Hydroxyphenyl derivatives **257** were only



minor products from a series of pyridazine 1-oxides, **256** (R = H, Me, Ph), and benzyne, from which 1-benzoxepines **258** were also obtained (25–70% yield).¹²³ The mechanism suggested to account for the formation of **258** is outlined in Scheme 24. In accord with this mechanism, 6-methylpyridazine 1-oxide (**255**) also gave a benzoxepine but no adduct analogous to **257**, and



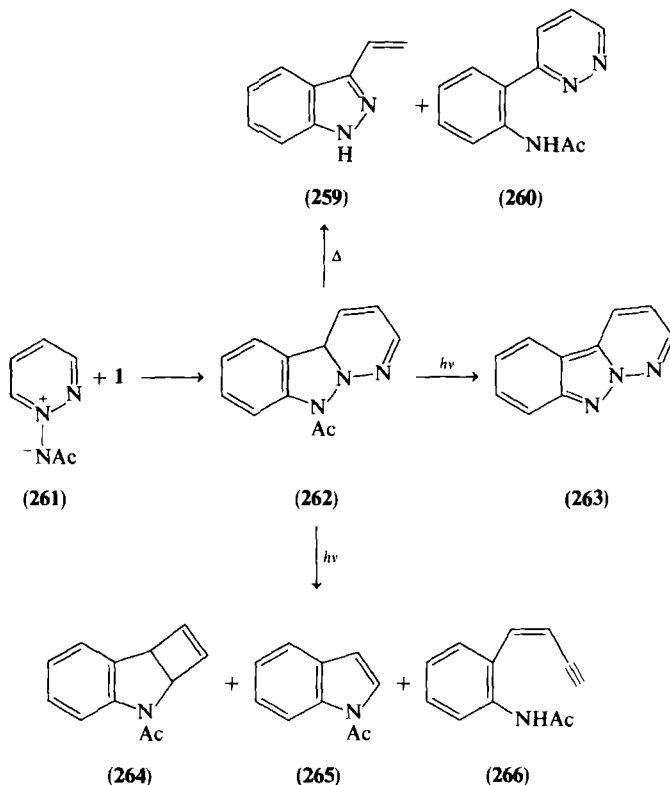
SCHEME 24

reaction of the related pyridazine imine **261** with benzyne furnished the 1,3-cycloadduct **262** (70%).¹²³ This was thermally converted into a mixture of the indazole **259** and the pyridazine **260**. The photochemical behavior of **262** is interesting: irradiation at 240 nm caused aromatization to the indazolo[2,3-*b*]pyridazine **263** in high yield, whereas irradiation of **262** at 360 nm

¹²² J. C. Mason and G. Tennant, *J. C. S., Chem. Commun.*, 218 (1972).

¹²³ H. Igeta, H. Arai, H. Hasegawa, and T. Tsuchiya, *Chem. Pharm. Bull.* **23**, 2791 (1975).

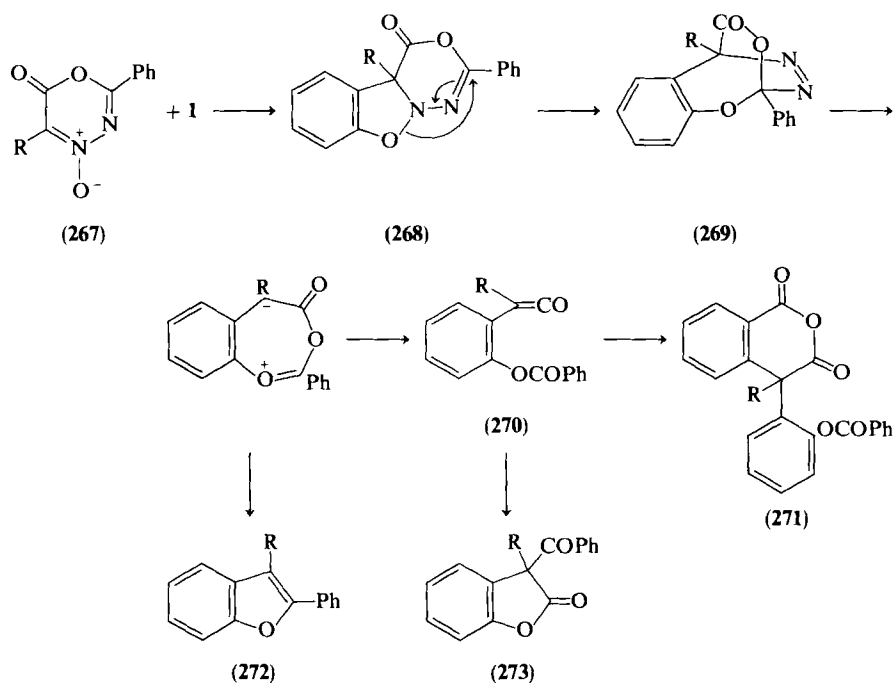
afforded not only **263** but also the indoles **264** and **265** and a small amount of the *o*-substituted acetanilide **266**. These transformations are summarized in Scheme 25; appropriate mechanisms are discussed in Ref. 123.



SCHEME 25

Decomposition of **4** in the presence of 1,3,4-oxadiazin-6-one 4-oxides, **267** (R = Me, Et, Ph), leads to the formation of benzofurans **272**, benzofuranones **273**, and the cyclic anhydrides **271**, all of which can be rationalized in terms of an initial 1,3-cycloaddition of benzyne to **267**, 1,3-sigmatropic rearrangement of **268** \rightarrow **269**, and subsequent decomposition steps as outlined in Scheme 26.¹²⁰ Formation of **271** requires a cycloaddition of the benzyne precursor **5** to the ketene intermediate **270**, which is supported by the observation of a similar capture of **5** by diphenylketene.

The variety and complexity of products described in these concluding examples drawn from the recent literature confirm the timeliness of this chapter on the reactions of benzyne with heterocyclic compounds, although we must still be far from the end of developments and discoveries in this field.



SCHEME 26

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Carbenes and Nitrenes in Heterocyclic Chemistry: Intramolecular Reactions

CURT WENTRUP

Department of Chemistry, University of Marburg, Marburg, West Germany

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I. Introduction

A. BACKGROUND

Several reviews on more or less specialized aspects of carbenes and nitrenes have appeared,¹⁻¹⁴ but none of them have been devoted to a survey of all the facets—synthetic and mechanistic—of such species in heterocyclic chemistry. The subject is far too vast for a complete coverage of all reactions, and it has been necessary, therefore, to limit the present review to intramolecular reactions. Since carbene and nitrene chemistry is dominated by molecular rearrangements, I found it necessary to organize this article in order of increasing complexity of rearrangements while maintaining as far as possible a reasonably logical sequence of increasing size and/or complexity of molecules synthesized as a result of the reactions.

The present review covers the literature up to about September, 1979. The accessible journals have also been covered up to the end of 1979 and a

¹ L. Horner and A. Christmann, *Angew. Chem., Int. Ed. Engl.* **2**, 599 (1963).

² R. A. Abramovitch and B. A. Davis, *Chem. Rev.* **64**, 149 (1964).

³ J. I. G. Cadogan *Q. Rev. Chem. Soc.* **22**, 222 (1968).

⁴ G. L'abbé, *Chem. Rev.* **69**, 345 (1969).

⁵ W. Lwowski, ed., "Nitrenes." Wiley (Interscience), New York, 1970.

⁶ R. K. Smalley and H. Suschitzky, *Chem. Ind. (London)*, 1338 (1970).

⁷ R. A. Abramovitch and E. P. Kyba, in "The Chemistry of the Azido Group" (S. Patai, ed.), Chapter 5. Wiley (Interscience), New York, 1971.

⁸ J. I. G. Cadogan, *Acc. Chem. Res.* **5**, 303 (1972).

⁹ T. Kametani, F. F. Ebetino, T. Yamanaka, and K. K. Nyu, *Heterocycles* **2**, 209 (1974).

¹⁰ C. Wentrup, *Top. Curr. Chem.* **62**, 1973 (1976).

¹¹ V. P. Semenov, A. N. Studenikov, and A. A. Potekhin, *Khim. Geterotsikl. Soedin.*, 291 (1978); 579 (1979).

¹² B. Iddon, O. Meth-Cohn, E. F. V. Scriven, H. Suschitzky, and P. T. Gallagher, *Angew. Chem., Int. Ed. Engl.* **18**, 900 (1979).

¹³ C. Wentrup, in "Reactive Intermediates" (R. A. Abramovitch, ed.), Vol. 1, Chapter 4 Plenum, New York, 1980.

¹⁴ W. M. Jones, in "Rearrangements in Ground and Excited States" (P. de Mayo, ed). Academic Press, New York, 1980.

few references from 1980 are included. Material which has previously been covered in depth will not be repeated, but reference to existing reviews will be given.

B. PHYSICAL PROPERTIES

ESR parameters for triplet carbenes¹⁵ and nitrenes¹⁶ have been summarized, and it has been shown that phenylnitrene is produced predominantly (87–88%) in the singlet state by direct photolysis of phenyl azide in low-temperature matrices.¹⁷ The first spectroscopic observation of a singlet nitrene has been reported: nanosecond-laser photolysis of 1-azidopyrene gives the S_0 nitrene (λ_{\max} 450 nm) which has a lifetime of 22 nsec at room temperature (in benzene) and 34 nsec at 77 K in rigid solution. At room temperature it decays to the triplet ground state (T_1 , λ_{\max} 415 nm) with a rate constant of about $4.4 \times 10^7 \text{ sec}^{-1}$. T_1 is formed directly by biacetyl sensitized photolysis of the azide. The lifetime of the excited triplet (T_2) was about 7 nsec. T_1 dimerizes to azopyrene.¹⁸

Other physical data or theoretical calculations will be quoted in the appropriate places in the following sections.

II. Vinylnitrenes, 2*H*-Azirines, and Iminocarbenes

A. NITRENES AND AZIRINES

The formation of 2*H*-azirines by thermolysis and photolysis of vinyl azides has been reviewed previously.^{19,20}

Smolinsky²¹ found that the gas-phase pyrolysis or liquid-phase photolysis of α -azidostyrenes (**1**) produced 50–60% yields of 3-aryl-2*H*-azirines (**2**) together with small amounts (5–10%) of ketenimines (**3**) (Eq. 1).

¹⁵ A. M. Trozzolo and E. Wasserman, in "Carbenes" (R. A. Moss and M. Jones, eds.), Vol. 2, p. 185. Wiley, New York, 1975; R. W. R. Humphreys and D. R. Arnold, *Can. J. Chem.* **55**, 2286 (1977).

¹⁶ E. Wasserman, *Prog. Phys. Org. Chem.* **8**, 319 (1971); J. H. Hall, J. M. Fargher, and M. R. Gisler, *J. Am. Chem. Soc.* **100**, 2029 (1978).

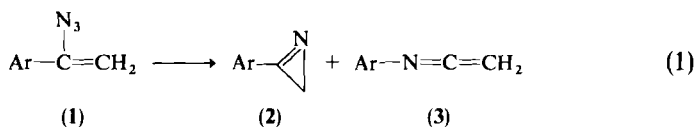
¹⁷ R. Reiser and L. J. Leyshon, *J. Am. Chem. Soc.* **93**, 4051 (1971).

¹⁸ M. Sumitani, S. Nagakura, and K. Yoshihara, *Bull. Chem. Soc. Jpn.* **49**, 2995 (1976).

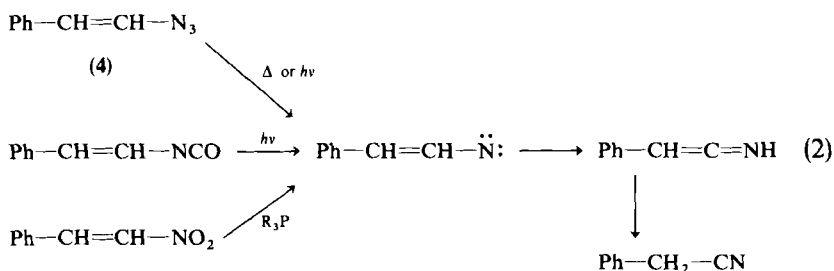
¹⁹ F. W. Fowler, *Adv. Heterocycl. Chem.* **13**, 45 (1971); G. Smolinsky and C. A. Pryde, in "The Chemistry of the Azido Group" (S. Patai, ed.), Chapter 10. Wiley (Interscience), New York, 1971; G. L'abbé and A. Hassner, *Angew. Chem., Int. Ed. Engl.* **10**, 98 (1971).

²⁰ G. L'abbé, *Angew. Chem., Int. Ed. Engl.* **14**, 775 (1975).

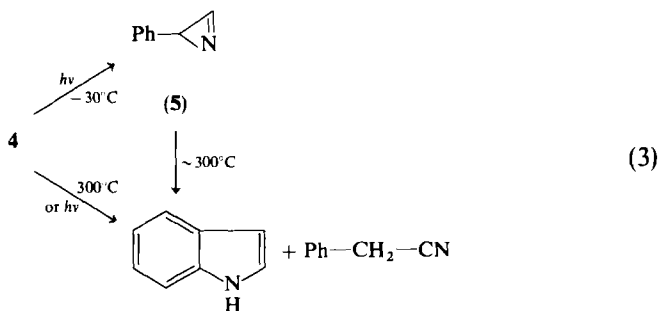
²¹ G. Smolinsky, *J. Am. Chem. Soc.* **83**, 4483 (1961); *J. Org. Chem.* **27**, 3557 (1962).



Boyer²² reported the formation of phenylacetonitrile by photolysis or pyrolysis of β -styryl azide (4), photolysis of β -styryl isocyanate, and triethyl phosphite deoxygenation of β -nitrostyrene. A nitrene mechanism was proposed (Eq. 2).



However, Isomura *et al.*²³ showed that an unstable azirine (5) is formed initially by photolysis or thermolysis of 4. The subsequent thermolysis (300°C, gas phase) or photolysis of the azirine gave a 1:1 mixture of phenylacetonitrile and indole (Eq. 3). Further examples of indole formation have been reported.^{23,24}



The generality of azirine formation from vinyl azides was demonstrated by Hassner and co-workers,²⁵ who also isolated the bicyclic azirine 7 from

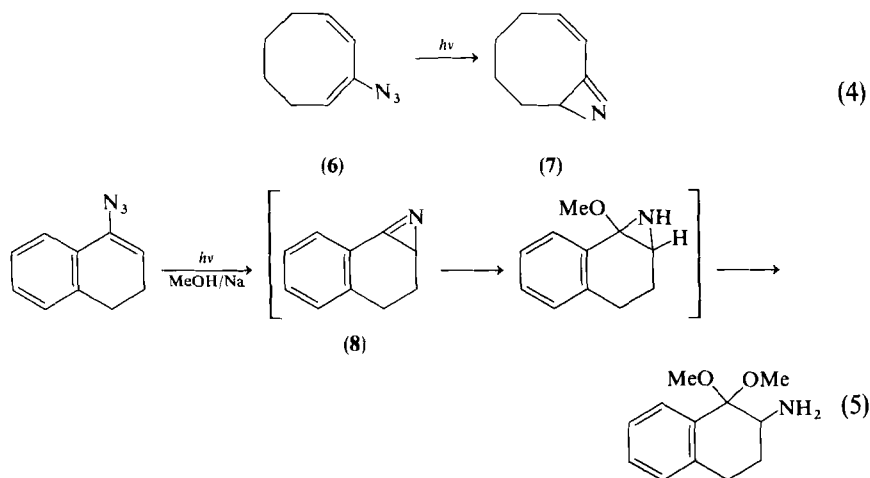
²² J. H. Boyer, W. E. Krueger, and G. J. Mikol, *J. Am. Chem. Soc.* **89**, 5504 (1967).

²³ K. Isomura, S. Kobayashi, and H. Taniguchi, *Tetrahedron Lett.*, 3499 (1968); K. Isomura, M. Okada, and H. Taniguchi, *ibid.*, 4073 (1969); K. Isomura, M. Okada, and H. Taniguchi, *Chem. Lett.*, 629 (1972); K. Isomura, K. Uto, and H. Taniguchi, *Chem. Commun.*, 664 (1977).

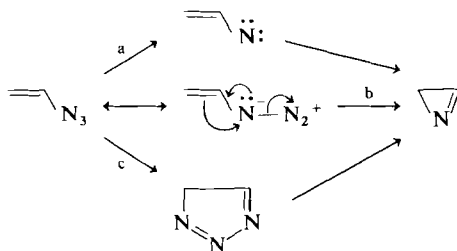
²⁴ D. J. Anderson, T. L. Gilchrist, G. E. Gymer, and C. W. Rees, *J. C. S. Perkin I*, 550 (1973); T. L. Gilchrist, C. W. Rees, and E. Stanton, *J. Chem. Soc. C*, 3036 (1971).

²⁵ D. J. Anderson and A. Hassner, *J. Org. Chem.* **38**, 2565 (1973).

the photolysis of the azide **6** (Eq. 4).²⁶ Evidence for the existence of the azirine **8** was obtained by trapping with methanol (Eq. 5).²⁶



The mechanism of azirine formation has been discussed by L'abbé.²⁰ *A priori*, the three paths shown in Scheme 1 can be considered. From a comparison of the activation parameters²⁷ for vinyl azide decomposition (E_a 26–30 kcal/mol, ΔS^\ddagger – 3 to + 5 eu) with those for aryl azides (E_a 35–39, ΔS^\ddagger ~ 18) it appears that the nitrene pathway a can be excluded, but a clear choice between paths b and c cannot be made at this time.²⁰

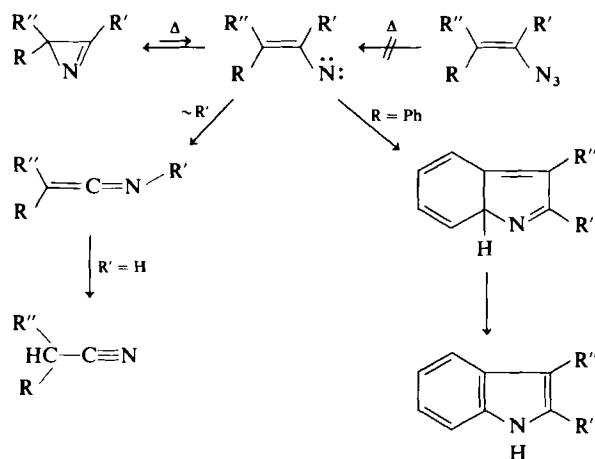


SCHEME 1

Although vinylnitrenes are not involved in the formation of 2*H*-azirines from vinyl azides, such nitrenes must be invoked in order to explain the further reactions of the azirines (Scheme 2). Thermal or photochemical ring opening of the azirine to a nitrene, and subsequent 1,2-shifts explain the formation of ketenimines and benzyl cyanides. A competing electrocyclization of the nitrene onto a phenyl substituent in the β -position leads to the

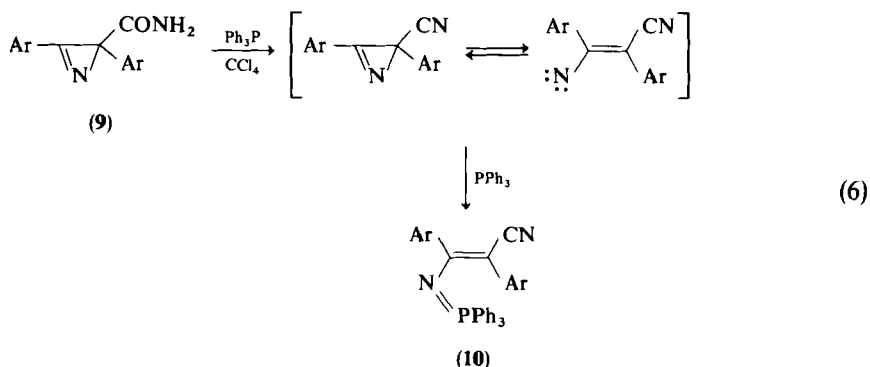
²⁶ A. Hassner and F. W. Fowler, *Tetrahedron Lett.*, 1545 (1967); *J. Am. Chem. Soc.* **90**, 2869 (1968).

²⁷ G. L'abbé and G. Mathys, *J. Org. Chem.* **39**, 1778 (1974).

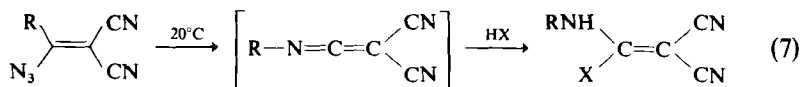


SCHEME 2

formation of indoles. Evidence for the formation of a nitrene from an azirine at a relatively low temperature (50–60°C) was adduced on the grounds of isolation of the iminophosphorane **10** from a treatment of the azirine **9** with triphenyl phosphite (Eq. 6). A nonnitrene path was shown to be unlikely.²⁸

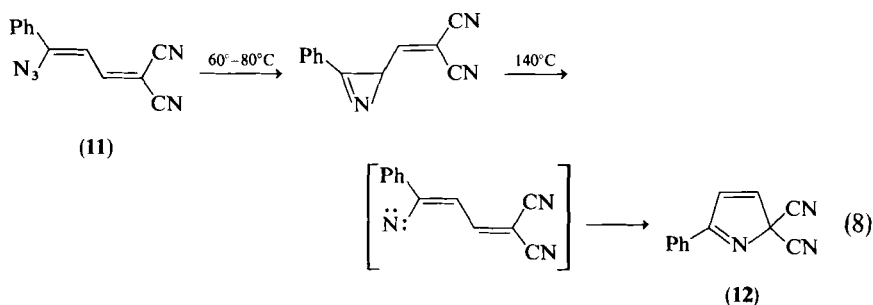


An even lower temperature is required for the rearrangement shown in Eq. (7).²⁹ If the reaction follows the normal course of Scheme 2, successive azirine and nitrene formation and rearrangement to the trappable ketenimine must already take place at 20°C.

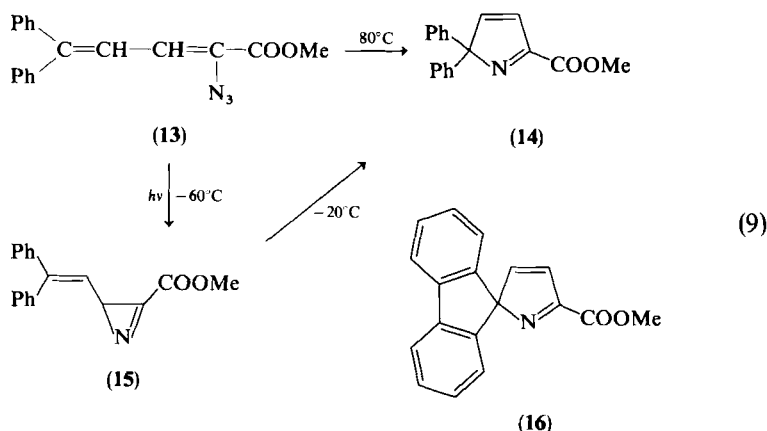


²⁸ T. Nishiwaki, *Chem. Commun.*, 565 (1972).

²⁹ K. Friedrich, *Angew. Chem., Int. Ed. Engl.* **6**, 957 (1967).



Conjugated dienyl azides cyclize to 2*H*-azirines, and these isomerize to 2*H*-pyrroles at higher temperatures. Thus, the stable 2,2-dicyano-2*H*-pyrrole **12** was formed in a two-stage thermolysis of the azide **11** (Eq. 8).³⁰ High yields (82–87%) of 2*H*-pyrroles **14** and **16** were obtained by thermal cyclization of the corresponding vinyl azides (e.g. **13**).³¹ The 2*H*-azirine **15** was



formed by photolysis at -60°C , and already rearranged to **14** at -20°C (Eq. 9). The azides (**17**) gave a mixture of pyrroles (**18**) and pyridines (**19**), the latter by nitrene insertion into the methyl group (Eq. 10).³¹ Applying the same principle, a number of 5-substituted pyrrole-2-carboxylic esters (**20**)^{31,32} and annelated pyrroles (Scheme 3)^{33–38} have been prepared, mostly

³⁰ K. Friedrich, G. Böck, and H. Fritz, *Tetrahedron Lett.*, 3327 (1978).

³¹ H. Hemetsberger, I. Spria, and W. Schönfelder, *J. Chem. Res. (S)*, 247 (1977).

³² J. P. Boukou-Poba, M. Farnier, and R. Guillard, *Tetrahedron Lett.*, 1717 (1979).

³³ H. Hemetsberger and D. Knittel, *Monatsh. Chem.*, **103**, 194 (1972).

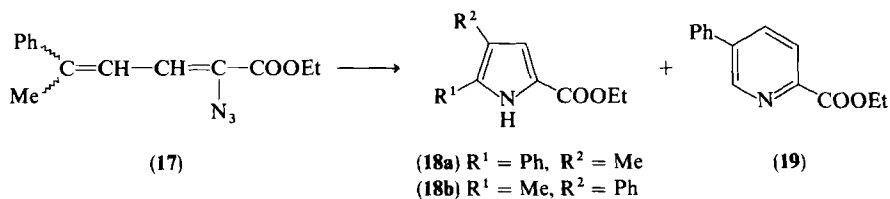
³⁴ A. Krutosikova, J. Kovac, and J. Kristofcak, *Collect. Czech. Chem. Commun.*, **44**, 1799 (1979).

³⁵ S. Soth, M. Farnier, and C. Paulmier, *Can. J. Chem.*, **56**, 1429 (1978).

³⁶ K. N. Java, S. Soth, and C. Paulmier, *C. R. Acad. Sci., Ser. C* **281**, 793 (1975).

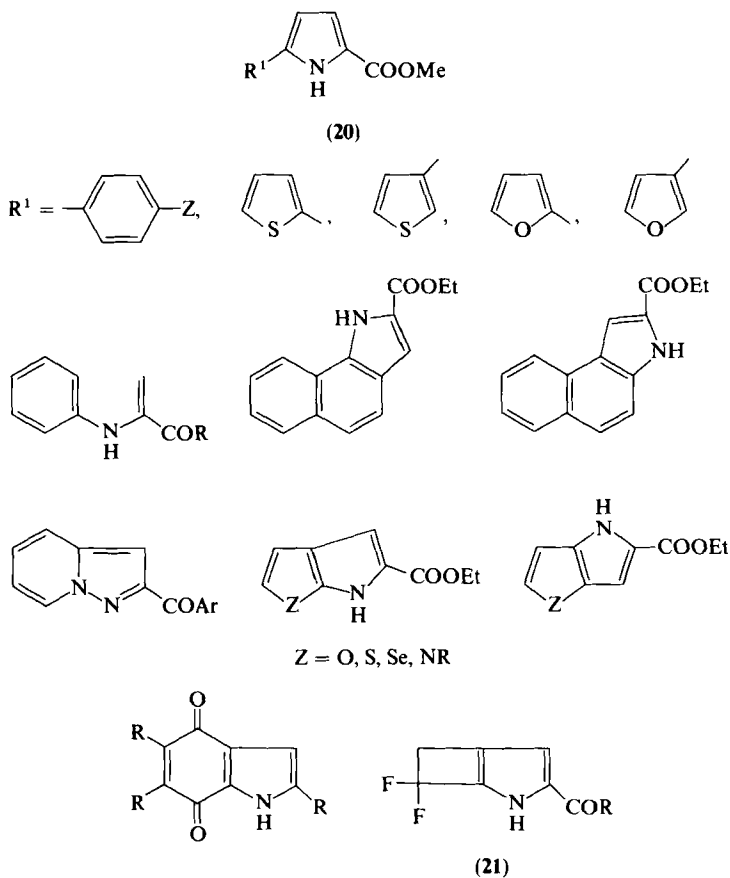
³⁷ P. Germeraad and H. W. Moore, *Chem. Commun.*, 358 (1973).

³⁸ G. Buhr, *Chem. Ber.*, **106**, 3544 (1973).



(10)

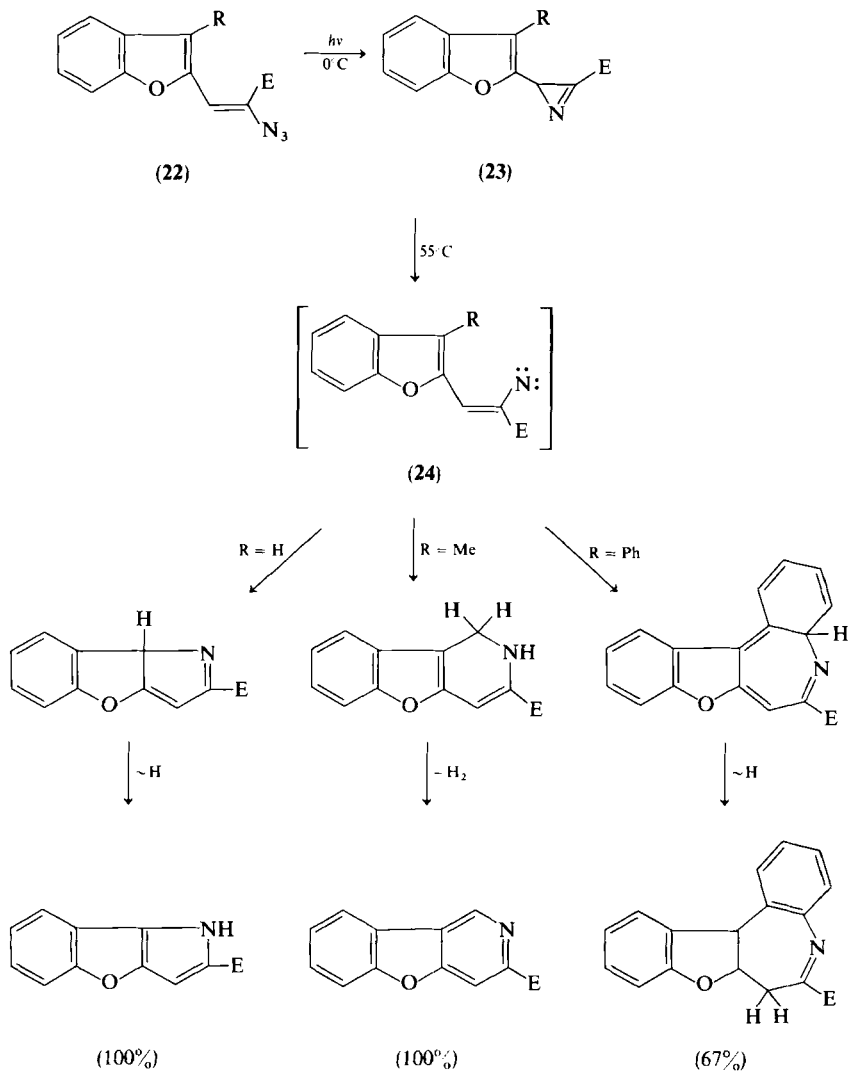
in excellent yields.* An exception is the cyclobutapyrrole **21** which was obtained in only 1–10% yield.³⁸



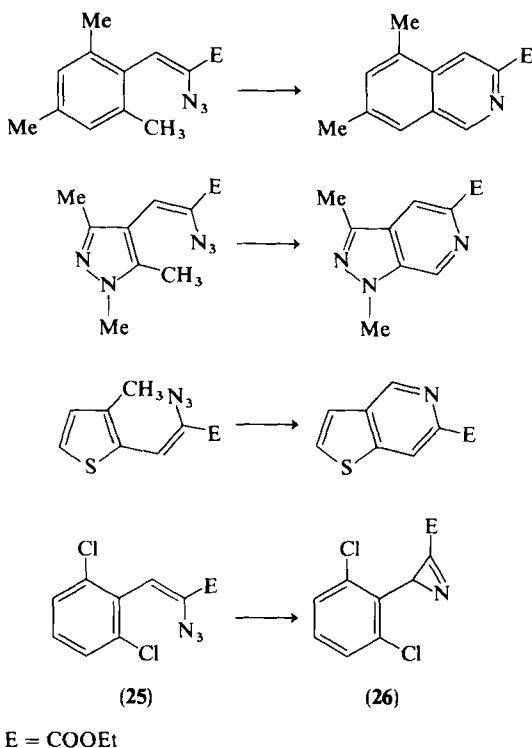
SCHEME 3

* For pyrrolo[3,2-*d*]thiazoles and pyrrolo[3,2-*d*]selenazoles, see A. Shafiee, A. Mazloumi, and V. I. Cohen, *J. Heterocycl. Chem.* **16**, 1563 (1979).

The whole range of vinylnitrene reactivity was demonstrated in the case shown in Scheme 4. The 2-(2-benzofuryl)-2*H*-azirine **23** was produced by photolysis of the azide **22** at 0°C. The azirine underwent thermal ring opening to the nitrene **24** at 55°C. Depending on the substituents, a condensed pyrrole, pyridine, or azepine was obtained, as illustrated in the scheme. The same



SCHEME 4



SCHEME 5

products were also formed by direct thermal decomposition of the azide **22**.³⁹

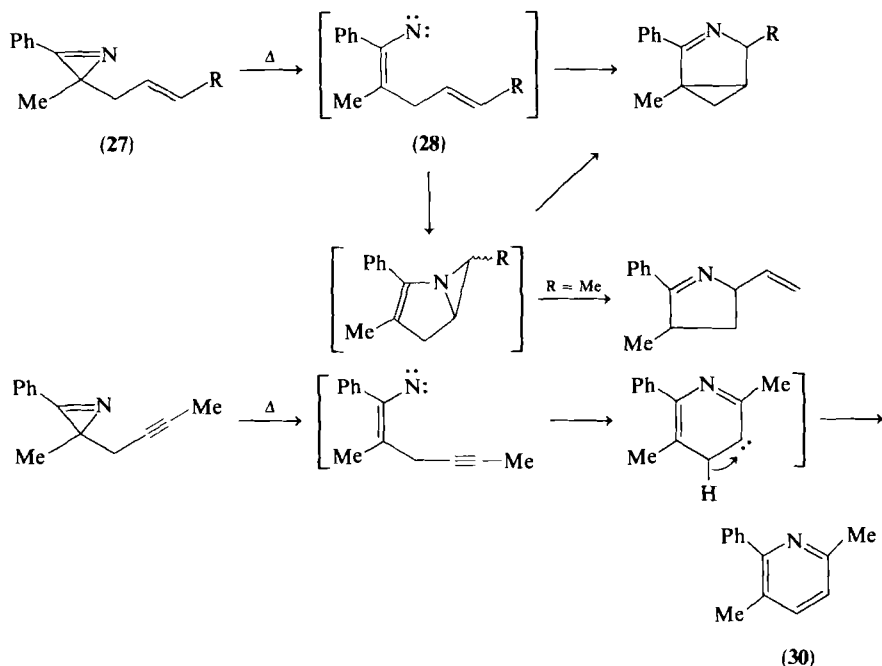
Further examples of the formation of annelated pyridines by nitrene insertion into methyl groups were obtained by pyrolysis of arylvinyl azides in toluene solution (Scheme 5).⁴⁰ Evidence that these reactions also take place via initially formed azirines was secured by the isolation of **26** from the pyrolysis of **25**.⁴⁰

Padwa and Carlsen have shown that nonconjugated dienylnitrenes (**28**) formed by thermolysis of 2*H*-azirines (**27**) undergo intramolecular addition to the remote double bond.⁴¹ Similarly, the pyridine **30** was obtained by flash vacuum pyrolysis of the acetylene **29** (Scheme 6).⁴¹

³⁹ K. Isomura, H. Taguchi, T. Tanaka, and H. Taniguchi, *Chem. Lett.*, 401 (1977); cf. K. Isomura, T. Tanaka, and H. Taniguchi, *ibid.*, 397 (1977).

⁴⁰ T. L. Gilchrist, C. W. Rees, and J. A. R. Rodrigues, *Chem. Commun.*, 627 (1979).

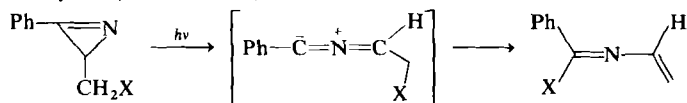
⁴¹ A. Padwa and P. H. J. Carlsen, *J. Org. Chem.* **43**, 2029 (1978).



B. IMINOCARBENE (NITRILE YLIDE) FORMATION

Bergman,⁴² Ghosez,⁴³ and co-workers discovered a new type of ring opening of azirines by pyrolysis in the gas phase, namely C—C bond cleavage to iminocarbenes (e.g., **33** from **31**⁴²), followed by a 1,4-hydrogen shift giving azadienes (**34**) (Scheme 7). The formation of azadienes by rearrangement of nitrile ylides had already been reported by Steglich and co-workers,⁴⁴ who studied the thermolysis of variously substituted oxazol-5(2*H*)-ones (**36**) in the condensed phase.*

* 1,4-Migration of groups other than hydrogen has been observed in photochemically generated nitrile ylides (iminocarbenes).^{44a}



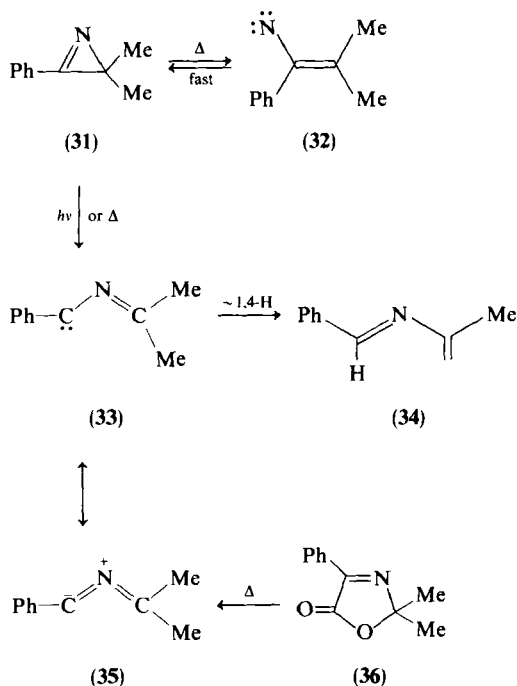
X = Cl, Br, OCOCH₃, OCOPh

⁴² L. A. Wendling and R. G. Bergman, *J. Org. Chem.* **41**, 831 (1976); *J. Am. Chem. Soc.* **96**, 308 (1974).

⁴³ A. Demoulin, H. Gorissen, A. M. Hesbain-Frisque, and L. Ghosez, *J. Am. Chem. Soc.* **97**, 4409 (1975).

⁴⁴ W. Steglich, P. Gruber, H.-U. Heininger, and F. Kneidl, *Chem. Ber.* **104**, 3816 (1971).

^{44a} A. Padwa, P. H. J. Carlsen, and A. Tremper, *J. Am. Chem. Soc.* **100**, 4481 (1978).



SCHEME 7

The iminocarbenes **33** (Scheme 7) may also be regarded as nitrile ylides (**35**). *Ab initio* calculations⁴⁵ indicate that nitrilium betaines are best described as hybrids of the bent dipolar and carbenic structures (e.g., **33** and **35**). Consequently, the generation of the nitrile ylide **35** in the gas phase should give the same product as obtained from the azirine **31**. This was confirmed by flash vacuum pyrolysis of the appropriate oxazol-5(2*H*)-one (**36**), which gave a quantitative yield of the azadiene **34**.⁴⁶

The azirine **31** (Scheme 7) is believed to be in preequilibrium with the nitrene **32**, the product of the normal C—N bond cleavage. In the absence of a β -phenyl substituent, **32** cannot form an indole. However, it remains unexplained that the ketenimine expected as a rearrangement product of **32** is not detectable.^{42,46} Possibly the ketenimine is formed, but decomposes

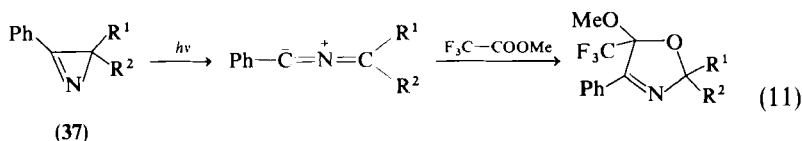
⁴⁵ P. Caramella and K. N. Houk, *J. Am. Chem. Soc.* **98**, 6397 (1976).

⁴⁶ H.-M. Berstermann, K.-P. Netsch, and C. Wentrup, *Chem. Commun.* 503 (1980).

^{46a} H.-M. Berstermann, Diploma Thesis. University of Marburg (1979).

due to chemical activation, which has been shown to be important in the pyrolysis of azirines.^{46*}

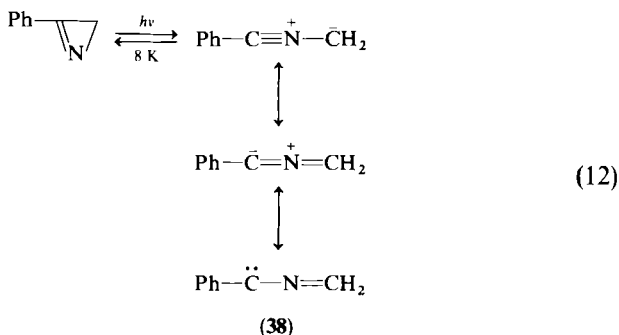
Carbon-carbon bond breaking is the normal path by *photolysis* of azirines.⁴⁷ UV spectroscopic evidence has been obtained for the formation of nitrile ylides on photolysis of the azirines **37** at -185°C .⁴⁸ The ylides can be trapped, for example, with methyl trifluoroacetate (Eq. 11).



(37)

$\text{R}^1, \text{R}^2 = \text{H}, \text{Ph}; \text{Ph}, \text{Ph}; \text{Me}, \text{Me}$

Similarly, benzonitrile ylide (**38**) was obtained by photolysis of 3-phenyl-2*H*-azirine at 8 K and characterized by its IR spectrum ($\nu_{\text{max}} 1930 \text{ cm}^{-1}$) (Eq. 12).⁴⁹



The dimethylamino-2*H*-azirine **39** undergoes exclusive C—C bond breaking by flash vacuum pyrolysis (350°C , 0.1 torr).⁵⁰ In this case, the intermediate iminocarbene (or nitrile ylide) **40** is stabilized by the amino group. Only the carbene product **42** and not the nitrene product **41** was isolated (Eq. 13).

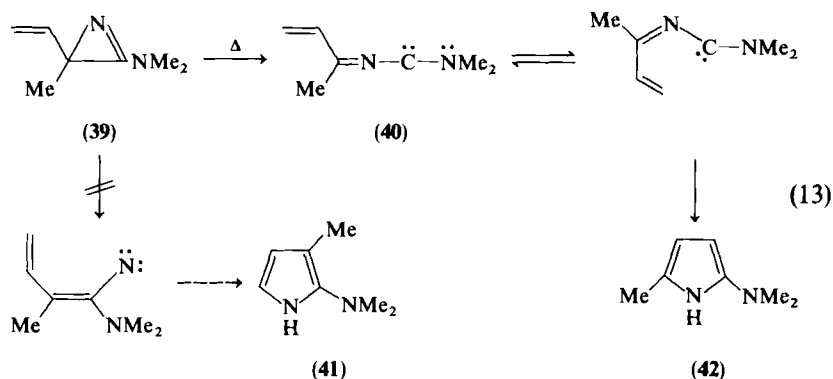
* Note added in proof: The ketenimine has now been identified (D. Laqua, unpublished results).

⁴⁷ P. Gilgen, H. Heimgartner, H. Schmid, and H.-J. Hansen, *Heterocycles* **6**, 143 (1977); K. Dietliker, W. Stegmann, and H. Heimgartner, *ibid.* **14**, 929 (1980).

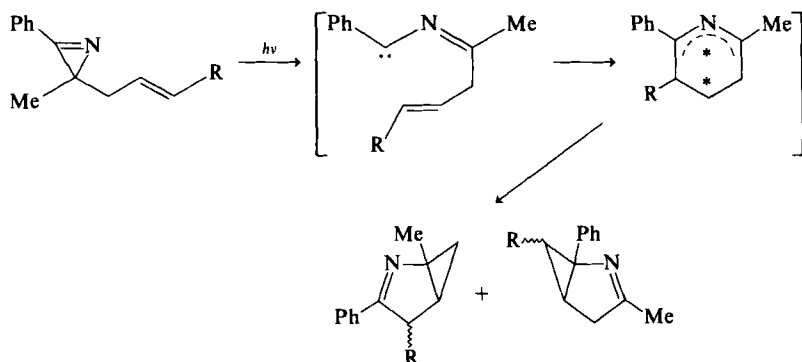
⁴⁸ A. Orahovats, H. Heimgartner, H. Schmid, and W. Heinzelmann, *Helv. Chim. Acta* **57**, 2626 (1974).

⁴⁹ O. L. Chapman and J.-P. LeRoux, *J. Am. Chem. Soc.* **100**, 282 (1978).

⁵⁰ L. Ghosez, A. Demoulin, M. Henriët, E. Sonveaux, M. van Meerssche, G. Germain, and J.-P. Declercq, *Heterocycles* **7**, 895 (1977).



Evidence for the carbenic nature of "nitrile ylides" formed by photolysis of azirines has been obtained from detailed mechanistic studies of intramolecular 1,1-cycloaddition reactions.⁵¹ It was concluded that these additions (Scheme 8) take place in a stepwise manner via diradical or zwitterionic intermediates.



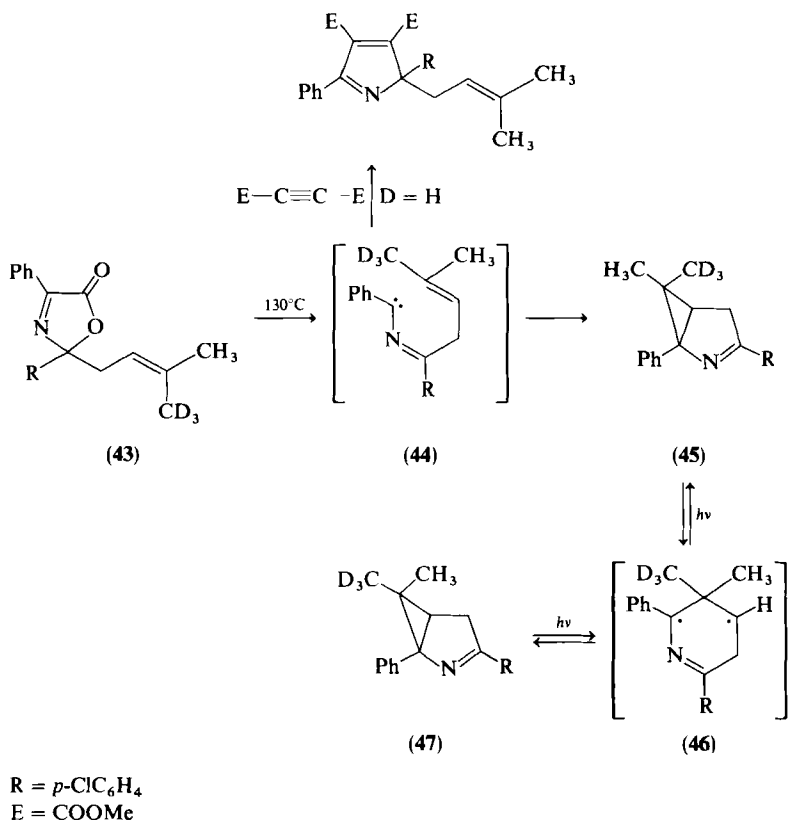
R = H, CH₃, Ph, COOCH₃

* = +, -, or ·

SCHEME 8

It would appear, however, that this stepwise process is a photochemical artifact, and that the "nitrile ylides" do indeed react as true carbenes, undergoing concerted 1,1-cycloaddition to the remote double bond. Fischer and

⁵¹ A. Padwa and P. H. J. Carlsen, *J. Am. Chem. Soc.* **99**, 1514 (1977); *J. Org. Chem.* **43**, 3757 (1978); A. Padwa and N. Kamigata, *J. Am. Chem. Soc.* **99**, 1871 (1977); A. Padwa and A. Ku, *ibid.* **100**, 2181 (1978); A. Padwa, P. H. J. Carlsen, and A. Ku, *ibid.* **99**, 2798 (1977); **100**, 3494 (1978); A. Padwa, *Acc. Chem. Res.* **9**, 371 (1976).



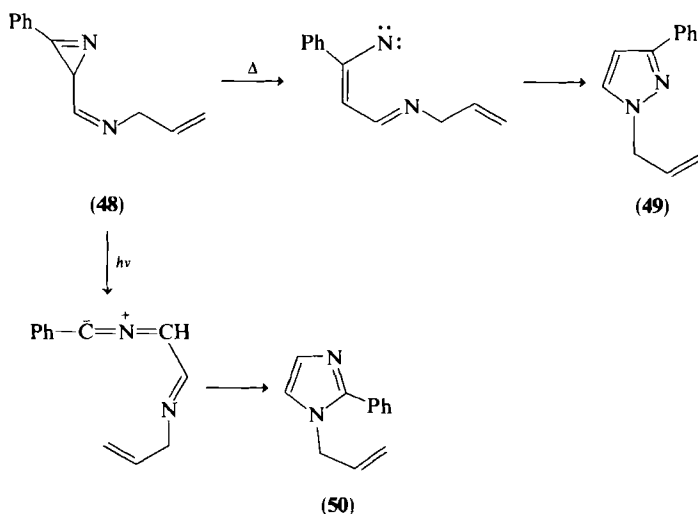
SCHEME 9

Steglich⁵² obtained the 2-azabicyclo[3.1.0]hex-2-en system (45) *stereospecifically* by *thermolysis* of the oxazolin-5-one 43, a method known to produce nitrile ylides. The intermediate 44 could be trapped with dimethyl acetylenedicarboxylate. Brief photolysis (4 min) of 45 caused epimerization to 47 (Scheme 9).⁵² Evidently, diradicals (or zwitterions) such as 46 are formed in a secondary photochemical process, which would also appear to apply to Scheme 8.

An example of the differing thermal and photochemical behavior of 2H-azirines is shown in Scheme 10. The starting material 48 rearranges to a pyrazole 49 thermally by a nitrene pathway; photochemically an imidazole (50) is formed, implying the nitrile ylide pathway.⁵³

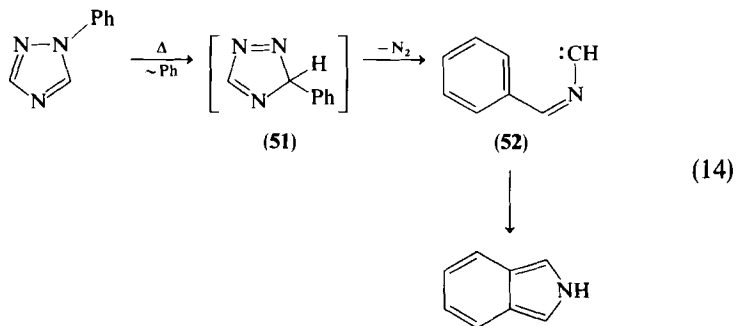
⁵² J. Fischer and W. Steglich, *Angew. Chem.* **91**, 168 (1979); *Angew. Chem., Int. Ed. Engl.* **18**, 167 (1979).

⁵³ A. Padwa, J. Smolanoff, and A. Tremper, *J. Org. Chem.* **41**, 543 (1976).

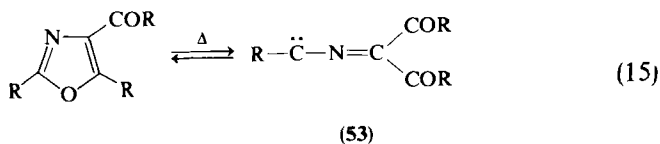


SCHEME 10

A species which may be described either as an iminocarbene⁵⁴ or a nitrile ylide (**52**) is formed by gas-phase pyrolysis of 1-phenyl-1,2,4-triazole (Eq. 14). The rearrangement, leading to isoindole, was rationalized in terms of a 1,5-phenyl shift followed by nitrogen extrusion from the 3*H*-triazole **51**.⁵⁴



It is also interesting to note that MINDO/3 calculations indicate that the Cornforth rearrangement (Eq. 15) proceeds via an intermediate (**53**) that has been variously described as a carbene and a zwitterionic species.⁵⁵



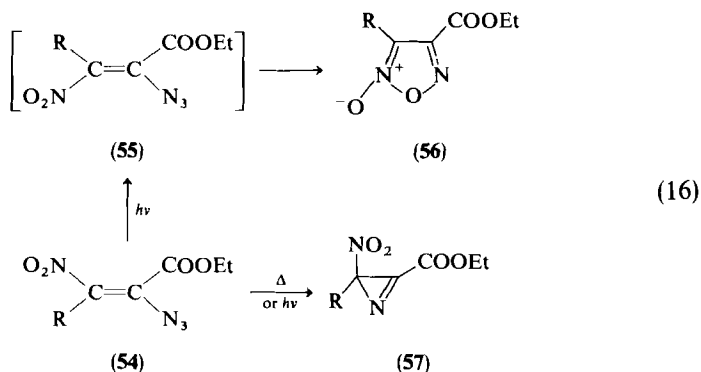
⁵⁴ T. L. Gilchrist, C. W. Rees, and C. Thomas, *J. C. S. Perkin I*, 12 (1975).

⁵⁵ M. J. S. Dewar, P. A. Spaninger, and I. J. Turchi, *Chem. Commun.*, 925 (1973).

Evidence has been obtained for the thermal isomerization of benzonitrile di(trifluoromethyl)methylide to 3-phenyl-2,2-di(trifluoromethyl)-2*H*-azirine.^{46a} Thus, the whole range of isomers—nitrile ylide, azirine, vinylnitrene, and ketenimine—is thermally accessible, and the first three are also thermally interconvertible.

C. CYCLIZATION ONTO NITRO GROUPS

Early attempts to prepare β -nitrovinyl azides led to the formation of furoxans.²⁰ The *E*- β -nitrovinyl azide **54** has however been isolated.⁵⁶ Its thermolysis in benzene afforded the azirine **57** in 60% yield; the same compound was obtained on photolysis, together with a small amount of the furoxan **56**, which is ascribed to photochemical *E*-*Z* isomerism, leading initially to **55** (Eq. 16). In the aromatic series it is known that *o*-nitroaryl azides undergo anchimerically assisted nitrogen elimination, giving benzofuroxans.⁵⁷



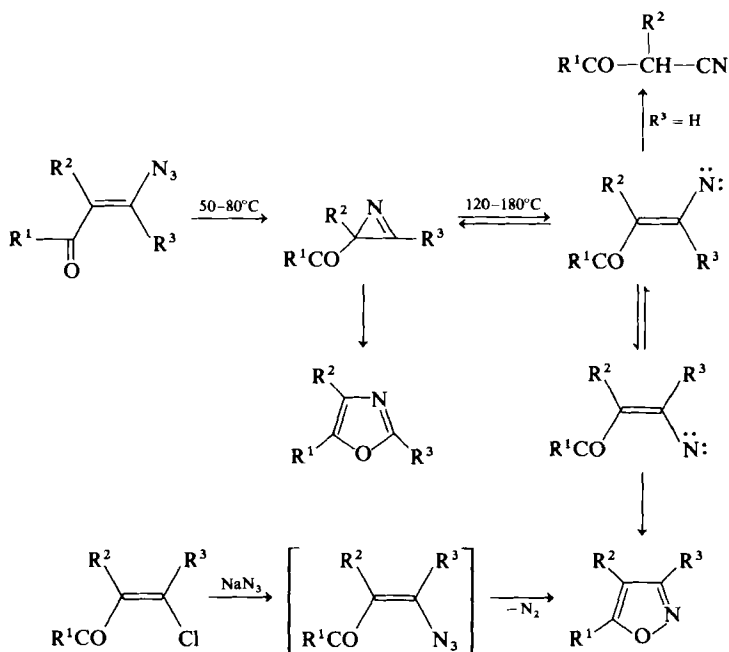
D. CYCLIZATION ONTO CARBONYL GROUPS

The behavior of β -oxovinyl azides is quite similar to that of the nitro compounds (Section II,C). The *E*-isomers form azirines, which in certain cases can be isolated.⁵⁸ At higher temperatures, rearrangement to oxazoles,

⁵⁶ C. Shin, Y. Yonezawa, K. Suzuki, and J. Yoshimura, *Bull. Chem. Soc. Jpn.* **51**, 2614 (1978).

⁵⁷ G. Bozhev, L. K. Dyll, and P. R. Sadler, *Aust. J. Chem.* **25**, 599 (1972); L. K. Dyll, *ibid.* **28**, 2147 (1975); **30**, 2669 (1977); L. K. Dyll and J. E. Kemp, *J. Chem. Soc. B*, 976 (1968).

⁵⁸ K. Isomura, Y. Hirose, H. Shuyama, S. Abe, G. Ayabe, and H. Taniguchi, *Heterocycles* **9**, 1207 (1978).



isoxazoles, or nitriles can take place. The *Z*- β -oxovinyl azides are unstable, decomposing in an anchimerically assisted concerted reaction (Scheme 11).^{20,58}

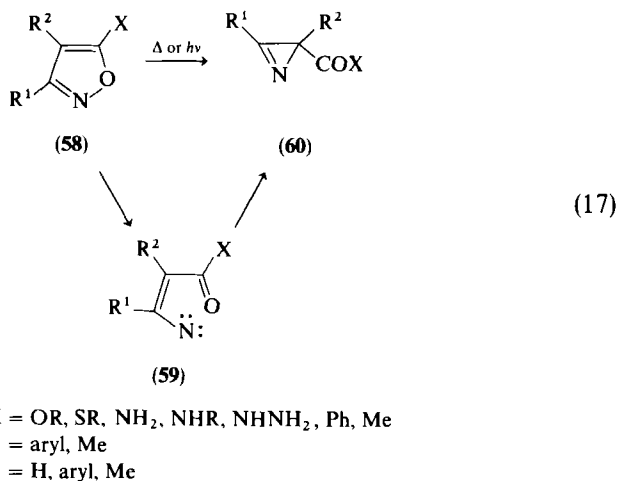
E. REVERSION OF ISOXAZOLES TO VINYLNITRENES

Thermolysis at 150–200°C or photolysis (>2800 Å) of a variety of isoxazoles (**58**) leads to cleavage of the N—O bond and formation of vinylnitrenes (**59**), which may also be formulated as mesomeric diradicals. In many instances, the latter cyclize to 2*H*-azirines (**60**) in synthetically useful yields (Eq. 17).⁵⁹

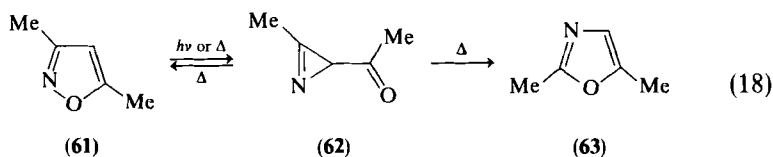
Several cases of isomerization of isoxazoles (e.g., **61**) to oxazoles (e.g., **63**) via 2*H*-azirines (e.g., **62**) have been reported.^{60,61} The azirine **62** was isolable,

⁵⁹ T. Nishiwaki, *Synthesis*, 20 (1975); T. Nishiwaki, K. Azechi, and F. Fujiyama, *J. C. S. Perkin I*, 1867 (1974); G. Adembri, A. Camparini, F. Ponticelli, and P. Tedeschi, *ibid.*, 971 (1977).

⁶⁰ D. A. Murature, J. D. Perez, M. M. De Bertorello, and H. Bertorello, *An. Asoc. Quim. Argent.* **64**, 337 (1976) [*CA* **89**, 128847 (1978)].



and underwent further rearrangement to **63** at 500–600°C in the gas phase (Eq. 18).⁶⁰ These reactions constitute the reverse of the reactions shown in Scheme 11.



The kinetics of a further series of isoxazole-2*H*-azirine rearrangements at 165–185°C has been investigated.⁶² The activation parameters for 3-phenyl-5-methoxyisoxazole ($\Delta H^\ddagger = 38 \pm 1$ kcal/mol; $\Delta S^\ddagger = 3.6 \pm 2$ eu) are in good accord with the postulated initial N—O bond breakage [$\text{DH}^\circ(\text{PhO}-\text{NR}_2) = 38\text{--}39$ kcal/mol⁶³]. The photochemical⁶⁴ and thermal⁶⁵ conversion of benzisoxazoles to benzoxazoles appears to involve an intermediate spiroazirine.

⁶¹ M. Maeda and M. Kojima, *J. C. S. Perkin I*, 239 (1977); G. J. de Voghel, T. L. Eggerichs, B. Clamot, and H. G. Viehe, *Chimia* **30**, 191 (1976); K. Dietliker, P. Gilgen, H. Heimgartner, and H. Schmid, *Helv. Chim. Acta* **59**, 2074 (1976); A. Padwa, E. Chen, and A. Ku, *J. Am. Chem. Soc.* **97**, 6484 (1975); K. Isomura, Y. Hirose, H. Shugama, S. Abe, G.-I. Ayabe, and H. Taniguchi, *Heterocycles* **9**, 1207 (1978).

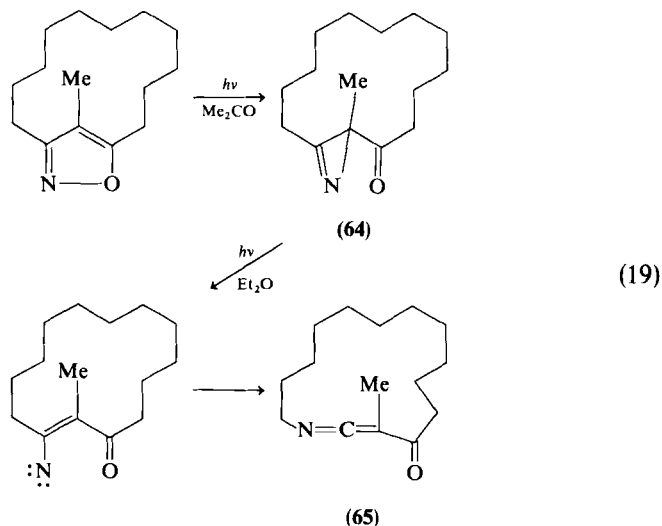
⁶² M. I. Komendantov, R. R. Bekmukhametov, and R. R. Kostikov, *Khim. Geterotsikl. Soedin.* **8**, 1053 (1978) [*CA* **89**, 214685 (1978)].

⁶³ K. W. Egger and A. T. Cocks, *Helv. Chim. Acta* **56**, 1516 (1973).

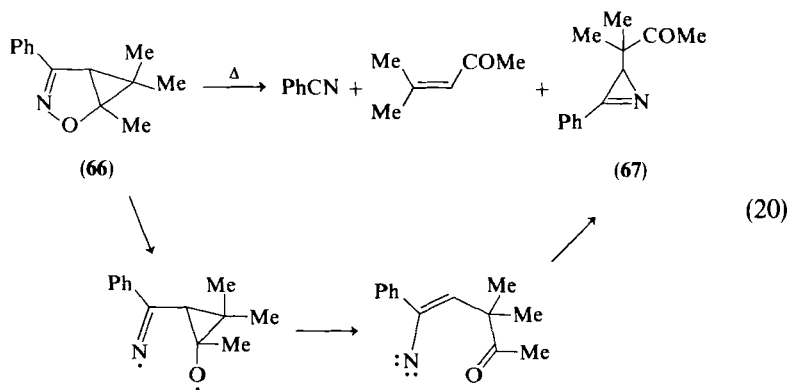
⁶⁴ K. H. Grellmann and E. Tauer, *J. Photochem.* **6**, 365 (1977).

⁶⁵ K. L. Davies, R. C. Storr, and P. J. Whittle, *Chem. Commun.*, 9 (1978).

An elegant application of the isoxazole–azirine rearrangement has been used in the generation of the fused azirine **64** which, on further photolysis, underwent ring expansion to the cyclic ketenimine **65** as shown in Eq. (19).⁶⁶



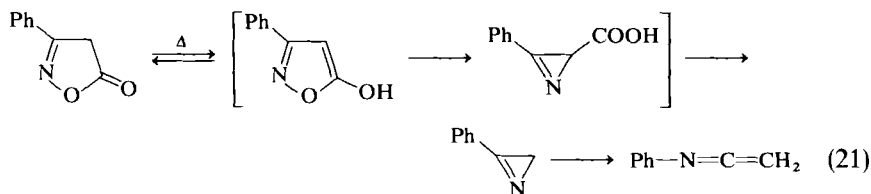
The formation of benzonitrile, methyl 2-methylpropenyl ketone, and the azirine **67** (ratio 2.3:2.3:1) in the thermolysis ($160\text{--}180^\circ\text{C}$, 7–10 torr) of the oxazoline **66** can be explained by initial N–O bond cleavage to biradical or nitrene intermediates (Eq. 20).⁶⁷



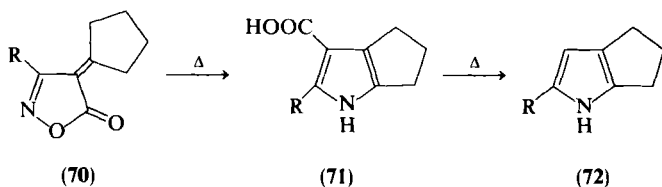
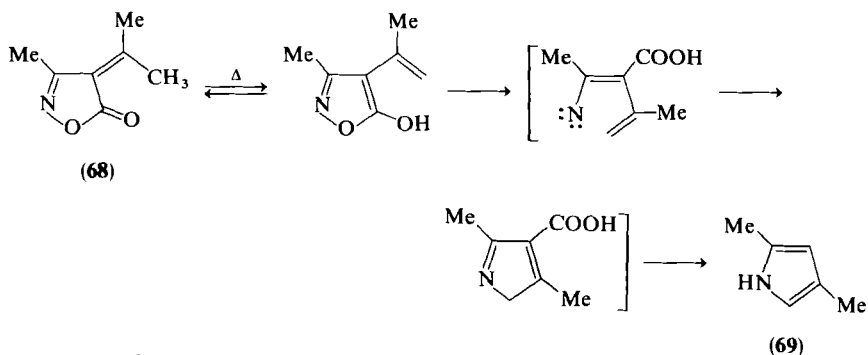
⁶⁶ S. Albanesi, A. Marchesini, and B. Gioia, *Tetrahedron Lett.*, 1875 (1979).

⁶⁷ L. G. Zaitseva, O. S. Chizhov, and I. G. Bolesov, *Zh. Org. Khim.* **11**, 1347 (1975); *J. Org. Chem. USSR (English Transl.)*, 1333 (1975) [*CA* **83**, 206142 (1975)].

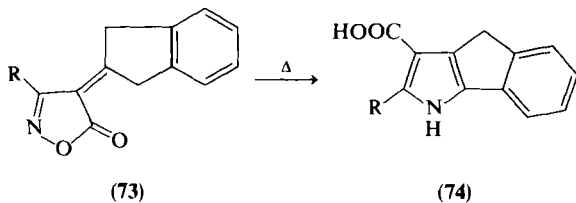
Isoxazol-5(4*H*)-ones rearrange to azirines and ketenimines on flash vacuum pyrolysis, probably via the 5-hydroxyisoxazoles (Eq. 21).⁶⁸



4-Methyleneisoxazol-5(4*H*)-ones (**68**, **70**, **73**) rearrange to pyrroles (**69**, **71**, **72**, **74**) at 800°C (10⁻³ torr).⁶⁸ Hydroxyisoxazoles and nitrenes are likely intermediates (Scheme 12).



R = Me or Ph



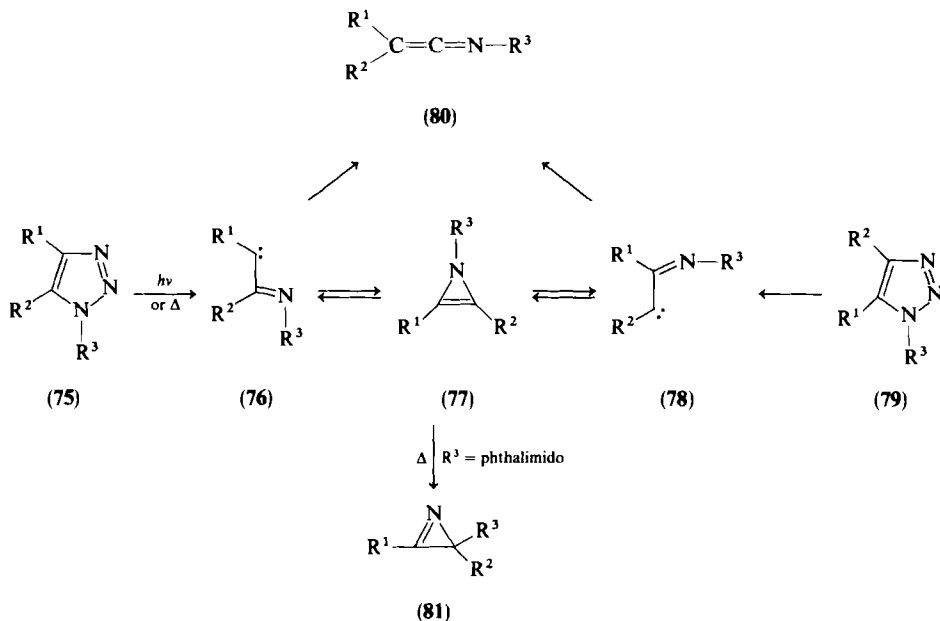
R = Me or Ph

SCHEME 12

⁶⁸ K.-P. Netsch and C. Wentrup, unpublished results (1979); H.-J. Wollweber, Ph.D. Thesis, University of Marburg (1980).

III. Imidoylcarbenes and 1*H*-Azirines

Imidoylcarbenes (**76** and **78**) are isomeric with vinylnitrenes and can in



principle cyclize to the formally antiaromatic 1*H*-azirines **77** or undergo a Wolff-type rearrangement (cf. Section IV) to ketenimines (**80**). Examples of the formation of **80** by photolysis of 1,2,3-triazoles were reported by Burgess *et al.*⁶⁹ (**75**, $\text{R}^1, \text{R}^2 = \text{H, Ph}$; $\text{R}^3 = \text{Ph}$). MINDO/3 and NDDO calculations indicate that the 1*H*-azirines **77** may be stable relative to the carbenes **76** and **78**, and hence an interconversion of the carbenes can be expected prior to the Wolff rearrangement.⁷⁰ The gas-phase pyrolysis of unsubstituted 1,2,3-triazole with direct microwave spectroscopy of the products did not allow the detection of 1*H*-azirine, acetonitrile being the major product.⁷¹ Evidence for carbene interconversion via 1*H*-azirines was, however, reported by Rees and co-workers who isolated the 2*H*-azirine **81** ($\text{R}^3 = \text{phthalimido}$), presumably formed by rearrangement of **77**.^{72,73}

Interconversion of the carbenes could also be demonstrated when $\text{R}^3 = \text{Me}$; in this case a rearrangement to isoquinolines took place, as exemplified

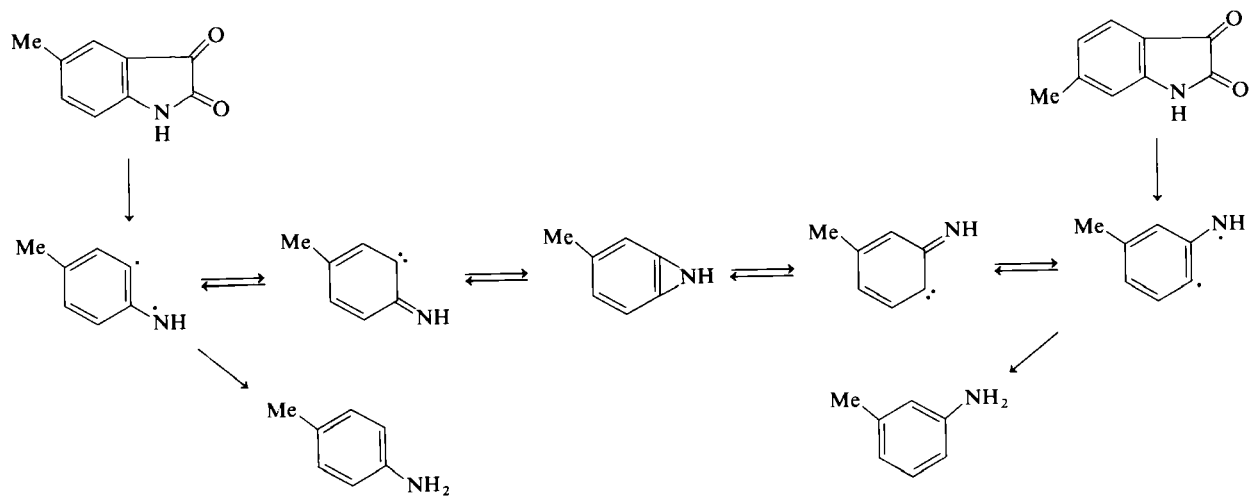
⁶⁹ E. M. Burgess, R. Carithers, and L. McCullagh, *J. Am. Chem. Soc.* **90**, 1923 (1968).

⁷⁰ M. J. S. Dewar and C. A. Ramsden, *Chem. Commun.*, 688 (1973).

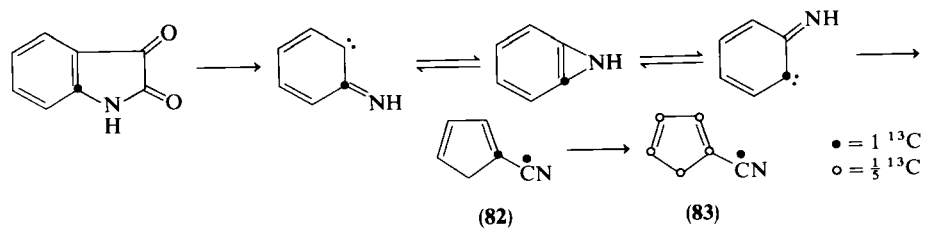
⁷¹ M. Winnewisser, J. Vogt, and H. Ahlbrecht, *J. Chem. Res. (S)*, 298 (1978).

⁷² T. L. Gilchrist, G. E. Gymer, and C. W. Rees, *Chem. Commun.*, 835 (1973).

⁷³ T. L. Gilchrist, G. E. Gymer, and C. W. Rees, *J. C. S. Perkin I*, 555 (1973).

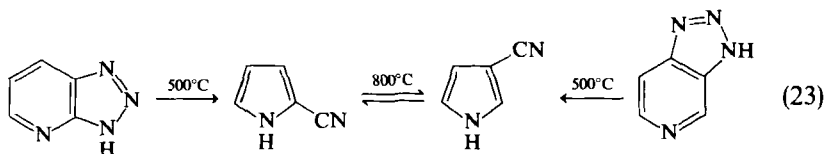


SCHEME 15

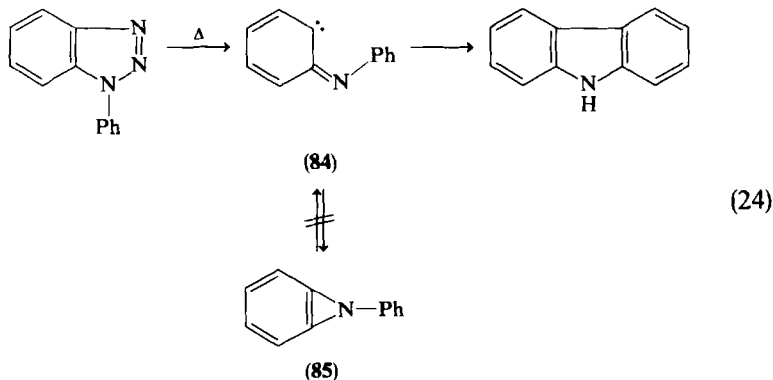


SCHEME 16

Ring contractions of this type, by pyrolysis of the corresponding triazoloarenes, have been used for the preparation of cyanoindenes and cyano-pyrroles (Eq. 23).⁷⁷



The Graebe-Ullmann synthesis of carbazoles by gas-phase pyrolysis⁸⁰⁻⁸³ or photolysis⁶⁹ of 1-aryl-1,2,3-benzotriazoles involves the cyclization of imidoylcarbenes (or the mesomeric 1,3-diradicals) onto aromatic rings (Eq. 24). This cyclization is apparently very rapid, for the use of substituted



derivatives showed that the carbene **84** does not interconvert with the 1H-benzazirine **85** prior to carbazole formation under either photochemical⁸⁴ or thermal⁷⁸ conditions.*

Variations of the carbazole synthesis include the use of 1-(2-pyridyl)-,^{85,86} 1-(2-pyrimidyl)-,⁸⁷ 1-(2-phenylquinazolin-4-yl)-,⁸⁸ and 1-(2-benzimidazolyl)-

* The triplet ground states of iminocyclohexadienylidenes of type **84** have been observed by ESR at 77 K and are best described as 1,3-diradicals. Triplet **84** decays (to carbazole) with an activation energy of about 5.2 kcal/mol [H. Murai, M. Torres, and O. P. Strausz, *J. Am. Chem. Soc.* **102**, 1421 (1980)].

⁸⁰ C. Graebe and F. Ullmann, *Justus Liebigs Ann. Chem.* **291**, 16 (1896).

⁸¹ F. Ullmann, *Justus Liebigs Ann. Chem.* **332**, 82 (1904); *Chem. Ber.* **31**, 1697 (1898).

⁸² W. Borsche and M. Feise, *Chem. Ber.* **40**, 378 (1907).

⁸³ W. Freudenberg, *Heterocycl. Comp.* **3**, 298 (1952).

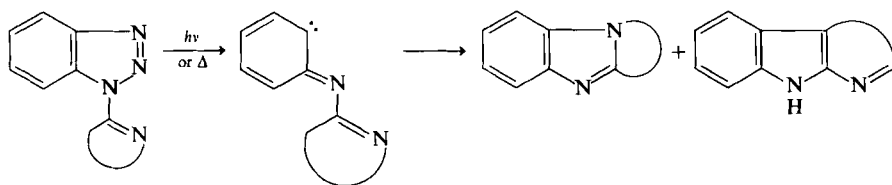
⁸⁴ M. Ohashi, K. Tsujimoto, and T. Yonezawa, *Chem. Commun.*, 1089 (1970).

⁸⁵ A. J. Hubert, *J. Chem. Soc. C*, 1334 (1969).

⁸⁶ P. Nantka-Namirski and J. Kalinowski, *Acta Pol. Pharm.* **31**, 137 (1974) [*CA* **81**, 152112 (1974)].

⁸⁷ A. J. Hubert and H. Reimlinger, *Chem. Ber.* **103**, 3811 (1970).

⁸⁸ A. J. Hubert, *J. Heterocycl. Chem.* **11**, 737 (1974).



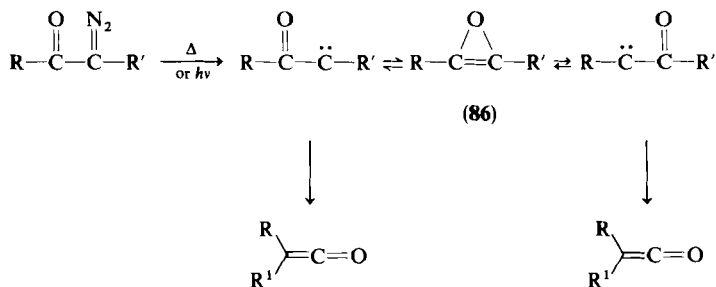
SCHEME 17

1,2,3-benzotriazoles⁸⁹ as shown in the general Scheme 17, as well as the formation of benzoxazoles and phenanthridinones from 1-acylbenzotriazoles.^{90,91}

IV. Oxocarbenes and Oxirenes

The Wolff rearrangement and the involvement of oxirenes (**86**) has been reviewed (Scheme 18).^{10,92,93}

Although theoretical calculations give conflicting answers regarding the relative energies of oxocarbenes and oxirenes,^{10,94} the fact that carbene-carbene interconversion can be observed under thermal conditions^{95,96} indicates that the oxirenes cannot be of significantly higher energy than the carbenes. Proof for the intermediate formation of oxirenes from acyclic



SCHEME 18

⁸⁹ J. de Mendoza and J. Elguero, *Bull. Soc. Chim. Fr.*, 2987 (1974).

⁹⁰ R. Huisgen and M. Seidel, *Chem. Ber.* **94**, 2509 (1961).

⁹¹ H. Meier and I. Menzel, *Justus Liebigs Ann. Chem.* **739**, 56 (1970).

⁹² H. Meier and K.-P. Zeller, *Angew. Chem., Int. Ed. Engl.* **14**, 32 (1975).

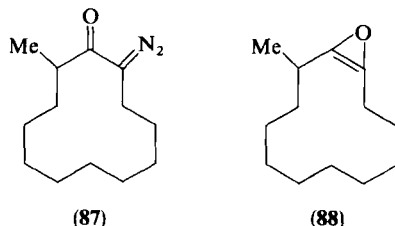
⁹³ W. Ried and H. Mengler, *Fortschr. Chem. Forsch.* **5**, 1 (1965).

⁹⁴ O. P. Strausz, R. K. Gosavi, A. S. Denes, and I. G. Csizmadia, *J. Am. Chem. Soc.* **98**, 4784 (1976); O. P. Strausz, R. K. Gosavi, and H. E. Gunning, *Chem. Phys. Lett.* **54**, 510 (1978).

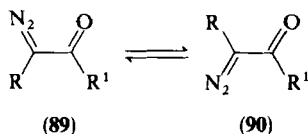
⁹⁵ S. A. Matlin and P. G. Sammes, *J. C. S. Perkin I*, 2623 (1972).

⁹⁶ U. Timm, K.-P. Zeller, and H. Meier, *Chem. Ber.* **111**, 1549 (1978).

oxocarbenes has been given using 1,2-hydrogen shifts in the rearranged and unrearranged carbenes,⁹⁵⁻⁹⁷ or by isotopic labeling.⁹⁸⁻¹⁰⁰ However, no evidence could be found for the involvement of oxirenes in the reactions of the naphthoquinodiazides,¹⁰¹ α -diazocyclohexanone,¹⁰² or α -diazohomoadamantanone.¹⁰³ Only in the case of 2-diazo-12-methylcyclododecan-1-one (**87**) was evidence obtained for partial reaction via the annelated oxirene **88** ($\sim 20\%$ thermally and 60% photochemically).⁹⁶



These results require some explanation. It has long been known that acyclic α -diazoketones and -esters exist predominantly in the s-cis form (**89**)¹⁰⁴⁻¹⁰⁸ although the energy barriers toward interconversion (**89** \rightleftharpoons **90**) are low.^{104,105,107}



It has also been suggested¹⁰⁴ that the s-cis forms (**89**) may undergo a concerted Wolff rearrangement due to the favorable anti relationship between the migrating group R' and the departing nitrogen molecule. Indeed, CIDNP evidence has been produced to demonstrate that diazoacetaldehyde

⁹⁷ R. A. Cormier, K. M. Freeman, and D. M. Schnur, *Tetrahedron Lett.*, 2231 (1977); R. A. Cormier, *ibid.* **21**, 2021 (1980).

⁹⁸ J. Fenwick, G. Frater, K. Ogi, and O. P. Strausz, *J. Am. Chem. Soc.* **95**, 124 (1973).

⁹⁹ K.-P. Zeller, H. Meier, H. Kolshorn, and E. Müller, *Chem. Ber.* **105**, 1875 (1972).

¹⁰⁰ K.-P. Zeller, *Chem. Ber.* **112**, 678 (1979).

¹⁰¹ K.-P. Zeller, *Chem. Ber.* **108**, 3566 (1975).

¹⁰² U. Timm, K.-P. Zeller, and H. Meier, *Tetrahedron* **33**, 453 (1977).

¹⁰³ K.-P. Zeller, *Z. Naturforsch., Teil B* **31**, 586 (1976); Z. Majerski and C. S. Redvanly, *Chem. Commun.*, 694 (1972).

¹⁰⁴ F. Kaplan and G. K. Meloy, *J. Am. Chem. Soc.* **88**, 950 (1966).

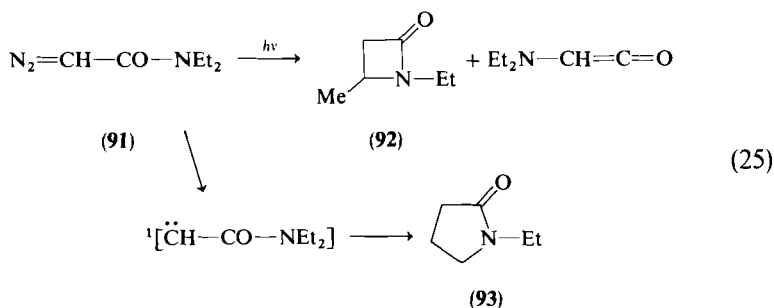
¹⁰⁵ C. Wentrup and H. Dahn, *Helv. Chim. Acta* **53**, 1637 (1970).

¹⁰⁶ S. Sorriso, G. Piazza, and A. Foffani, *J. Chem. Soc. B*, 805 (1971).

¹⁰⁷ G. Paliani, S. Sorriso, and R. Cataliotti, *J. C. S. Perkin II*, 707 (1976).

¹⁰⁸ I. G. Csizmadia, S. A. Houlden, O. Meresz, and P. Yates, *Tetrahedron* **25**, 2121 (1969).

undergoes a concerted (i.e., noncarbene) Wolff rearrangement in solution.¹⁰⁹ Moreover, it has been shown that α -diazamides (**91**) undergo intramolecular photochemical C—H insertion to give the lactam **92** together with the ketene in a *noncarbene process*.¹¹⁰ From the effects of sensitizers and quenchers it



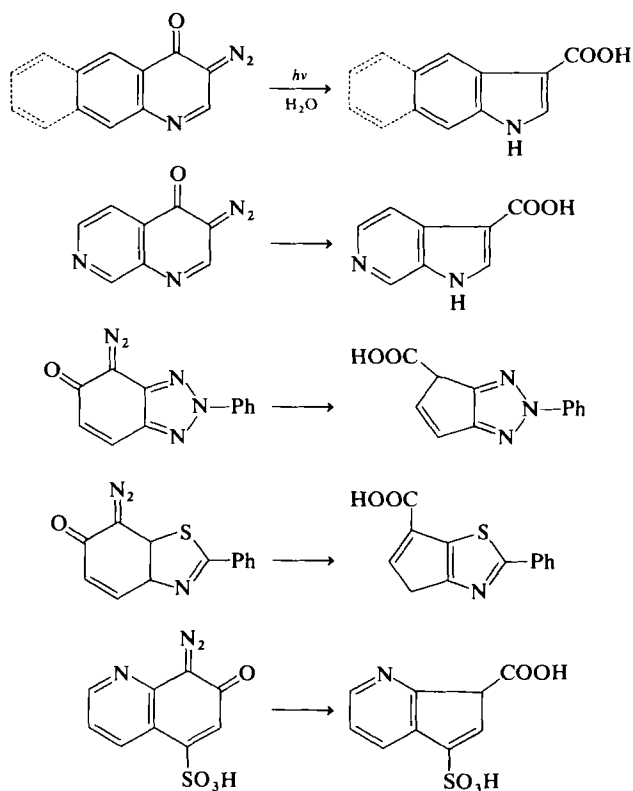
was concluded that the Wolff rearrangement as well as the formation of **92** involve the excited singlet state of the diazo compound (Eq. 25).¹¹⁰ In contrast, the γ -lactam **93** was formed from the singlet carbene. It was further suggested that such processes are conformationally dependent, i.e., the *s*-cis forms (**89**) are the ones undergoing direct reaction (substitution and Wolff rearrangement), and the *s*-trans forms (**90**) give free carbenes.¹¹⁰

On the other hand, the labeling experiments cited above (Scheme 18) constitute almost irrefutable evidence for the existence of the free oxocarbenes in all those cases where oxirene participation has been demonstrated. Notably, this has been the case most frequently in photochemical and in thermal gas-phase reactions, i.e., under conditions of relatively high energy where the interconversion **89** \rightleftharpoons **90** will be rapid and the equilibrium concentration of **90** relatively high. Some Wolff rearrangement can now take place in a concerted manner in the *s*-cis forms (**89**), while the *s*-trans forms (**90**) will give free carbenes. The latter also undergo the Wolff rearrangement, but after interconversion with oxirenes according to Scheme 18. All the rigid cyclic diazoketones cited^{101–103} are conformationally constrained to the planar *s*-cis forms; hence no oxirene participation was observed. The situation is quite different in **87**: here conformational constraints *disfavor* the *s*-cis form. Consequently, carbenic Wolff rearrangement is observed photochemically as well as thermally.

Apart from the well-known Arndt–Eistert homologization of carboxylic acids and the many and varied intermolecular reactions of the ketenes formed

¹⁰⁹ H. D. Roth and M. L. Manion, *J. Am. Chem. Soc.* **98**, 3392 (1976); H. D. Roth, *Acc. Chem. Res.* **10**, 85 (1977).

¹¹⁰ H. Tomioka, H. Kitagawa, and Y. Izawa, *J. Org. Chem.* **44**, 3072 (1979).



SCHEME 19

in Wolff rearrangements, these reactions are also of value for the synthesis of aromatic and heteroaromatic compounds. Süss has shown that *o*-quinone diazides photolytically rearrange to ketenes, which with water or nucleophiles afford carboxylic acid derivatives of cyclopentadiene, indene, pyrrole, and other heterocyclic systems (Scheme 19).¹¹¹⁻¹¹⁴

Related rearrangements of naphthoquinonediazides have been carried out both thermally¹¹⁵ and photolytically.¹¹⁶ The formation of indole-3-

¹¹¹ O. Süss, *Justus Liebigs Ann. Chem.* **556**, 56, 85 (1944); **557**, 237 (1947); **579**, 133 (1953).

¹¹² O. Süss, M. Glos, K. Möller, and H.-D. Eberhardt, *Justus Liebigs Ann. Chem.* **583**, 150 (1953).

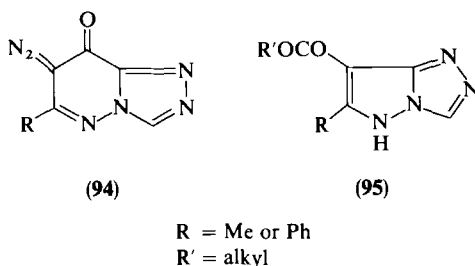
¹¹³ O. Süss and K. Möller, *Justus Liebigs Ann. Chem.* **593**, 91 (1955); **599**, 233 (1956).

¹¹⁴ O. Süss, H. Steppan, and R. Dietrich, *Justus Liebigs Ann. Chem.* **617**, 20 (1958).

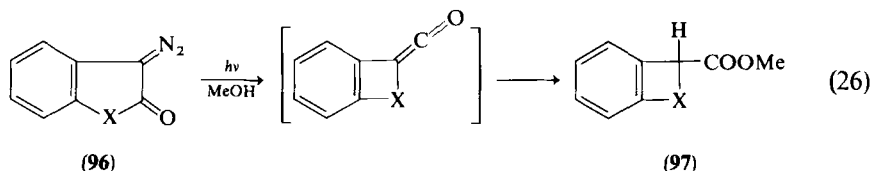
¹¹⁵ P. A. S. Smith and W. L. Berry, *J. Org. Chem.* **26**, 27 (1961).

¹¹⁶ K. Nakamura, S. Udagawa, and K. Honda, *Chem. Lett.* 763 (1972).

carboxylic acid derivatives has been studied in detail by Tisler and co-workers.¹¹⁷ The diazoketones **94** are transformed into pyrazolotriazoles (**95**) by photolysis in the presence of alcohols.¹¹⁸ Ring contraction in diazopyrimidinediones and diazopyridazinediones has also been reported.¹¹⁹



The first stable benzothiete (**97**, X = S) was prepared by Wolff rearrangement of the diazoketone **96** (X = S); benzoxetes and benzazetes can be prepared analogously (Eq. 26).¹²⁰



X = NH, NMe, O, S

A few selected examples of other uses of oxocarbenes (or carbenoids) in the synthesis of heterocyclic compounds are shown in Scheme 20.¹²¹⁻¹²⁴ Applications of intramolecular addition reactions of α -oxocarbenes in the synthesis of natural products have been summarized.¹²⁵

¹¹⁷ J. T. Carlock, J. S. Bradshaw, B. Stanovnik, and M. Tisler, *J. Heterocycl. Chem.* **14**, 519 (1977); *J. Org. Chem.* **42**, 1883 (1977); B. Stanovnik, M. Tisler, and J. T. Carlock, *Synthesis*, 754 (1976).

¹¹⁸ B. Stanovnik, M. Tisler, B. Kirn, and I. Kovac, *J. Heterocycl. Chem.* **16**, 195 (1979).

¹¹⁹ B. Stanovnik, M. Tisler, and E. Voncina, *Heterocycles* **12**, 761 (1979); B. Stanovnik, M. Tisler, J. Bradac, B. Budic, B. Koren, and B. Mozetic-Rescic, *ibid.*, 457.

¹²⁰ E. Voigt and H. Meier, *Chem. Ber.* **110**, 2242 (1977).

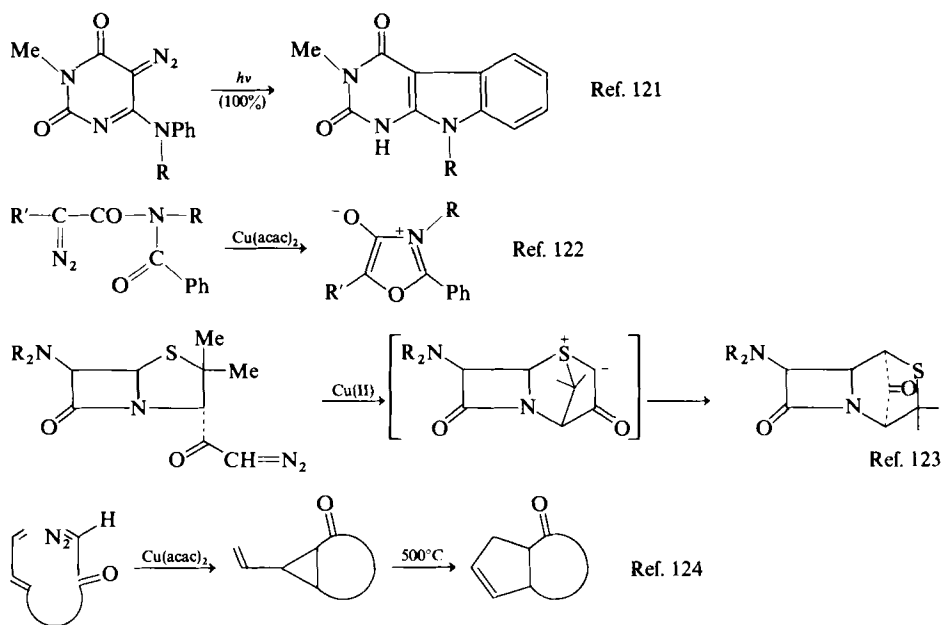
¹²¹ Y. Sakuma and F. Yoneda, *Heterocycles* **6**, 1911 (1977).

¹²² M. Hamaguchi, *Chem. Commun.*, 247 (1978).

¹²³ I. Ernest, *Tetrahedron* **33**, 547 (1977), and literature therein.

¹²⁴ T. Hudlicky, J. P. Sheth, V. Gee, and D. Barnvos, *Tetrahedron Lett.*, 4889 (1979).

¹²⁵ S. D. Burke and P. A. Grieco, *Org. React.* **26**, 361 (1979).



SCHEME 20

V. Thioxocarbenes, Thiirenes, and Selenium Analogs

Early work on these species has been summarized.¹⁰ In the meanwhile, thiirene (**99**) and several substituted derivatives,^{126–129} as well as seleniirene,¹²⁶ have been matrix-isolated and observed by IR spectroscopy on photolysis of 1,2,3-thiadiazoles or selenadiazoles (Eq. 27). The same species are also obtained by photolysis of vinylene trithiocarbonates (**100**).^{128*}

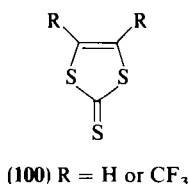
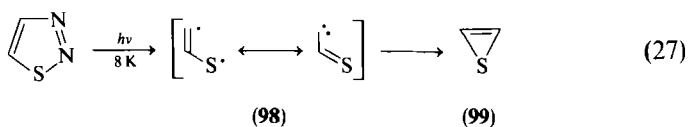
* The involvement of 2-phenylthiirene in both thermolysis and photolysis of 5-phenyl-1,2,3-thiadiazole has been ascertained by ¹³C labeling [U. Timm, U. Merkle, and H. Meier, *Chem. Ber.* **113**, 2519 (1980)].

¹²⁶ A. Krantz and J. Laureni, *J. Am. Chem. Soc.* **99**, 4842 (1977); J. Laureni, A. Krantz, and R. A. Hajdu, *ibid.* **98**, 7872 (1976).

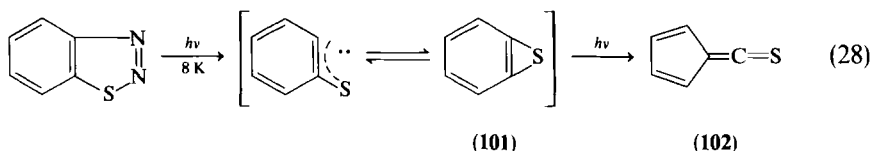
¹²⁷ M. Torres, A. Clement, J. E. Bertie, H. E. Gunning, and O. P. Strausz, *J. Org. Chem.* **43**, 2490 (1978).

¹²⁸ M. Torres, A. Clement, J. E. Bertie, H. E. Gunning, and O. P. Strausz, *Nouv. J. Chim.* **3**, 149 (1979).

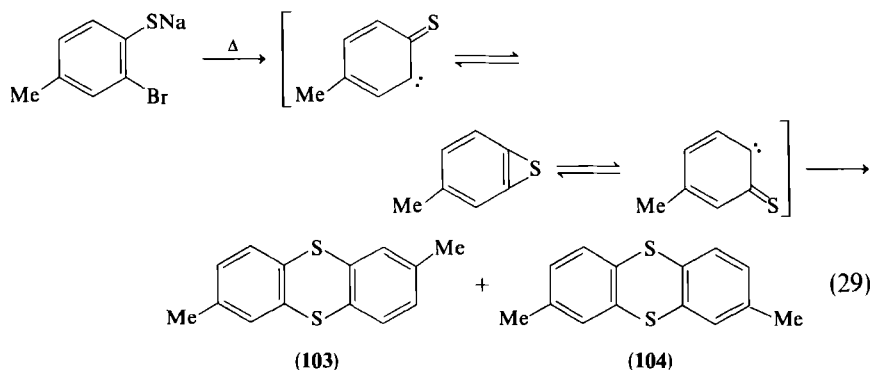
¹²⁹ A. Krantz and J. Laureni, *J. Org. Chem.* **44**, 2730 (1979); B. A. Hess, L. J. Schaad, and C. S. Ewig, *J. Am. Chem. Soc.* **102**, 2507 (1980).



The photolysis of benzothiadiazole at 8 K gave a species which has not yet been fully identified but may have been benzothiirene (**101**). Further irradiation caused rearrangement to the thioketene **102** (Eq. 28).¹²⁷



Previous evidence for the existence of benzothiirene in solution had been reported by Cadogan *et al.*¹³⁰ who obtained a mixture (about 1:1) of thianthrenes **103** and **104** by thermolysis of sodium *o*-bromobenzenethiolate (Eq. 29).



Using similar criteria, the involvement of benzothiirene in the thermolysis and photolysis of 1,2,3-benzothiadiazole was indicated by the isolation of mixed thianthrenes or thiophenols,¹³¹ although a report to the contrary has

¹³⁰ J. I. G. Cadogan, J. T. Sharp, and M. J. Trattles, *Chem. Commun.*, 900 (1974).

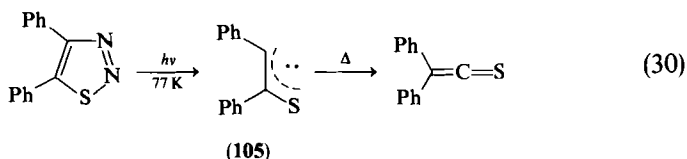
¹³¹ T. Wooldridge and T. D. Roberts, *Tetrahedron Lett.*, 2643 (1977); R. C. White, J. Scoby, and T. D. Roberts, *ibid.*, 2785 (1979).

also appeared.¹³² A thiirene was not involved in the thermolysis or photolysis of 4,5,6,7-tetrahydrocyclohexa[1,2-*d*][1,2,3]thiadiazole.¹³³

Thus, while definitive proof is still lacking, the existence of benzothiirene, like that of 1*H*-benzazirine⁷⁹ (Section III), is fairly certain. In contrast, all attempts to find evidence for benzoxirene as an intermediate in similar reactions have failed (thermolysis of sodium *o*-bromophenoxide,¹³⁰ and flash pyrolysis of *o*-quinonediazide,¹³⁴ salicylic acid¹³⁴ or its methyl ester,¹³⁵ including methyl [1-¹³C]salicylate¹³⁶). Calculations indicate, however, that the energy differences between oxirene and formylcarbene on the one hand, and thiirene and thioformylcarbene on the other, are fairly similar.¹³⁷

Flash thermolysis is a convenient way of producing thioketenes from 1,2,3-thiadiazoles.^{134,138,139} Thiirenes are formed prior to thioketenes in the gas phase¹⁴⁰ or matrix¹²⁷ photolysis of 1,2,3-thiadiazoles.

The triplet thiobenzoylphenylcarbene (**105**) has been detected by ESR spectroscopy in the photolysis of 4,5-diphenyl-1,2,3-thiadiazole.¹⁴¹ Diphenylthioketene was formed on warming to room temperature (Eq. 30).



Interestingly, thioketenes are also formed in good yields by flash thermolysis (530–590°C/10⁻³ torr) of isothiazoles. Thioxocarbenes and/or thiirenes were postulated as intermediates.¹⁴²

Flash pyrolysis of 1,2,3-selenadiazoles gives selenoketenes which are stable at -196°C and were identified by IR and microwave spectroscopy.¹⁴³ On warming, dimerization occurred (Eq. 31).

¹³² L. Benati, D. C. Montecocchi, and G. Zanardi, *J. Org. Chem.* **42**, 575 (1977).

¹³³ U. Timm, H. Bühl, and H. Meier, *J. Heterocycl. Chem.* **15**, 697 (1978).

¹³⁴ R. Schulz and A. Schweig, *Tetrahedron Lett.*, **59** (1979).

¹³⁵ H. F. Grützmacher and J. Hübner, *Justus Liebigs Ann. Chem.* **748**, 154 (1971); 793, (1973).

¹³⁶ C. Thétaz, Ph.D. Thesis, pp. 54–59. University of Lausanne (1977).

¹³⁷ O. P. Strausz, R. K. Gosavi, F. Bernardi, P. G. Mezey, J. D. Goddard, and I. G. Csizmadia, *Chem. Phys. Lett.* **53**, 211 (1978).

¹³⁸ G. Seybold and C. Heibl, *Chem. Ber.* **110**, 1225 (1977); *Angew. Chem., Int. Ed. Engl.* **14**, 248 (1975); E. Schaumann, J. Ehlers, and H. Mrotzek, *Justus Liebigs Ann. Chem.*, 1734 (1979).

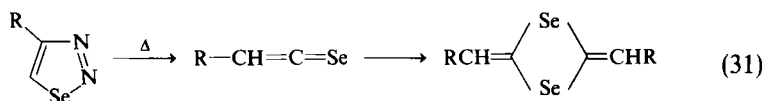
¹³⁹ H. Bock, B. Solouki, G. Bert, and P. Rosmus, *J. Am. Chem. Soc.* **99**, 1663 (1977).

¹⁴⁰ J. Font, M. Torres, O. P. Strausz, and H. E. Gunning, *J. Org. Chem.* **43**, 2487 (1978).

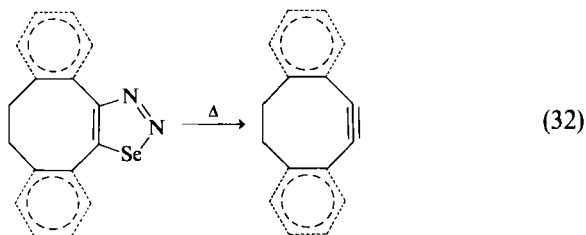
¹⁴¹ H. Murai, M. Torres, and O. P. Strausz, *J. Am. Chem. Soc.* **101**, 3976 (1979).

¹⁴² G. E. Castillo and H. E. Bertorello, *J. C. S. Perkin I*, 325 (1978).

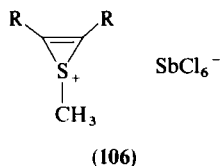
¹⁴³ A. Holm, C. Berg, C. Bjerre, B. Bak, and J. Svanholt, *Chem. Commun.*, 99 (1979); B. Bak, O. J. Nielsen, J. Svanholt, and A. Holm, *Chem. Phys. Lett.* **53**, 374 (1978); **55**, 36 (1978).



The interesting capacity of annelated selenadiazoles to lose nitrogen and selenium,¹⁴⁴ possibly via intermediate selenoxocarbenes (Eq. 32) is also of potential use for the production of novel heterocyclic compounds.



Finally, it should be noted that *S*-methylthiirenium salts (**106**) are stable below -40°C ; **106** (*R* = *tert*-butyl) is even stable at room temperature.¹⁴⁵ This may be ascribed to reduced antiaromaticity of the thiirene ring.



VI. Acylnitrenes and Thio Analogs

Acylnitrenes (oxonitrenes) are the aza analogs of oxocarbenes. Much evidence has been produced to show that the Curtius and related rearrangements leading to isocyanates do not involve acylnitrenes^{146,147} (see below, however). In contrast, alkoxycarbonylnitrenes are formed both thermally and photolytically from the corresponding azides, but such nitrenes rarely undergo the Curtius rearrangement.¹⁴⁸

¹⁴⁴ H. Meier and K.-P. Zeller, *Angew. Chem., Int. Ed. Engl.* **16**, 835 (1977); H. Bühl, U. Timm, and H. Meier, *Chem. Ber.* **112**, 3728 (1979).

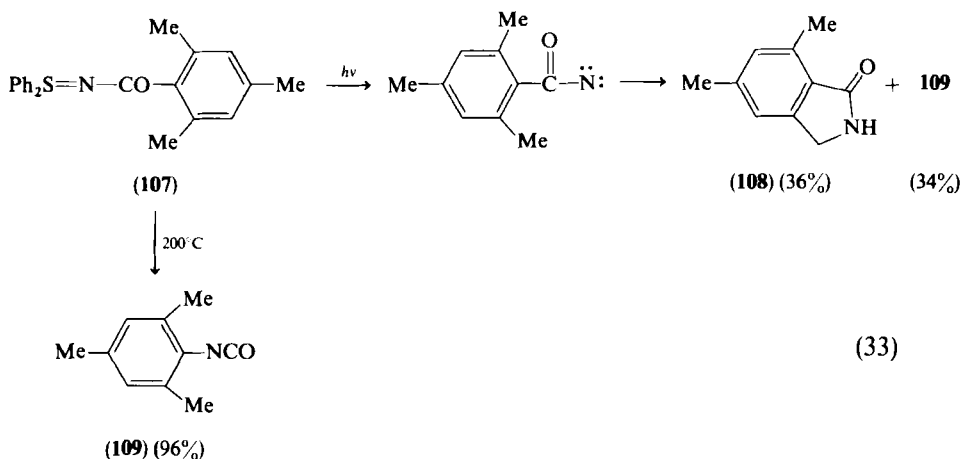
¹⁴⁵ G. Capozzi, V. Lucchini, G. Modena, and P. Scrimin, *Tetrahedron Lett.*, 911 (1977).

¹⁴⁶ W. Lwowski, *Angew. Chem., Int. Ed. Engl.* **6**, 897 (1967).

¹⁴⁷ S. Linke, G. T. Tisue, and W. Lwowski, *J. Am. Chem. Soc.* **89**, 6308 (1967); G. T. Tisue, S. Linke, and W. Lwowski, *ibid.*, 6303.

¹⁴⁸ R. Puttner, W. Kaiser, and K. Hafner, *Tetrahedron Lett.*, 4315 (1968).

Acylnitrenes are formed by *photolysis* of acyl azides and react intramolecularly to form lactams.¹⁴⁹⁻¹⁵⁴ Evidence was adduced that it is a singlet nitrene which cyclizes to the lactam **108** on photolysis of the sulfilimine **107**.¹⁵⁵ Thermolysis gave only mesityl isocyanate (**109**).¹⁵⁵ Isocyanates often,¹⁵⁶ but not always¹⁵⁷ accompany photolyses of acyl azides; but generally this is thought to be a nonnitrene process (see below, however).



Eibler and Sauer¹⁵⁸ demonstrated with the aid of competition experiments that the same intermediate, in all likelihood the benzoylnitrene, was formed by photolysis of **110**–**112** (Eq. 34). Phenyl isocyanate was formed both thermally and photolytically from all three precursors, but no evidence for a nitrene was obtained under thermal conditions.

¹⁴⁹ W. Lwowski, in "Nitrenes" (W. Lwowski, ed.), Chapter 6. Wiley (Interscience), New York, 1970.

¹⁵⁰ O. E. Edwards, in "Nitrenes" (W. Lwowski, ed.), Chapter 7. Wiley (Interscience), New York, 1970.

¹⁵¹ W. Lwowski, in "Reactive Intermediates" (M. Jones and R. A. Moss, eds.), Chapter 6. Wiley, New York, 1978.

¹⁵² W. Lwowski and S. Linke, *Justus Liebigs Ann. Chem.*, 8 (1977).

¹⁵³ P. F. Alewood, M. Benn, J. Wong, and A. J. Jones, *Can. J. Chem.* **55**, 2510 (1977).

¹⁵⁴ J. J. Wright and J. B. Morton, *Chem. Commun.*, 668 (1976).

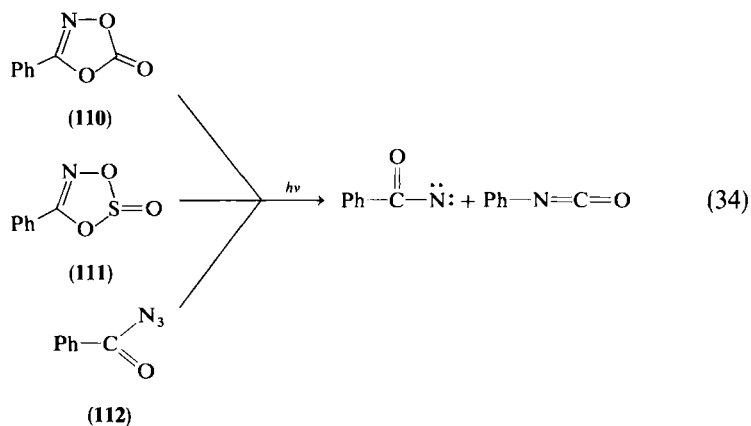
¹⁵⁵ N. Furukawa, T. Nishio, M. Fukumura, and S. Oae, *Chem. Lett.*, 209 (1978); N. Furukawa, M. Fukumura, T. Nishio, and S. Oae, *Phosphorus Sulfur* **5**, 231 (1978).

^{155a} N. Furukawa, M. Fukumura, T. Nishio, and S. Oae, *J. C. S. Perkin I*, 96 (1977).

¹⁵⁶ V. P. Semenov, A. N. Studenikov, A. D. Bespalov, and K. A. Ogloblin, *Zh. Org. Khim.* **13**, 2202 (1977); V. P. Semenov, A. N. Studenikov, A. P. Prosykina, and K. A. Ogloblin, *ibid.*, 2207.

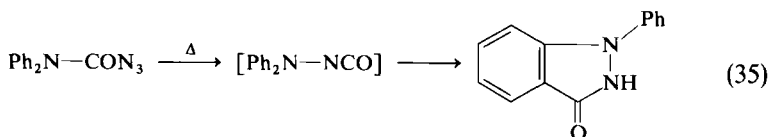
¹⁵⁷ A. F. M. Fahmy, G. H. Sayed, A. A. Hamed, and A. A. Morsy, *Indian J. Chem., Sect. B* **16**, 869 (1978).

¹⁵⁸ E. Eibler and J. Sauer, *Tetrahedron Lett.*, 2565 (1974).



The photolysis of aminimides produces acylnitrenes, which have usually been trapped in intermolecular reactions.^{151,159} Again, isocyanates often accompany the reactions. The thermolysis of 2,4,6-triphenylpyridine *N*-acylimines at 170–250°C affords isocyanates in good yields.¹⁶⁰

Even if no nitrenes are produced as intermediates, the isocyanates formed in Curtius-type rearrangements are of value for the synthesis of heterocyclic compounds. For example, transient isocyanates cyclize unto azine rings, giving imidazoazines (Scheme 21).¹⁶¹ *N,N*-Diphenylcarbamoyl azide rearranges thermally to 1-phenylindazolone (Eq. 35) via the elusive diphenylamino isocyanate.¹⁶² Further examples have been summarized by Reichen.¹⁶³



In the case of the oxocarbenes (Section IV) proof for the existence of free carbenes could be obtained whenever the participation of oxirenes in the

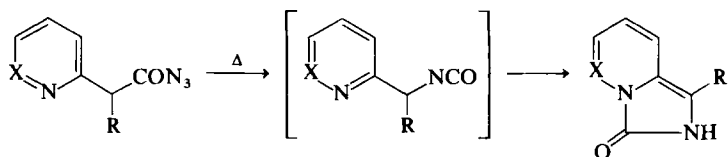
¹⁵⁹ A. R. Lepley, in "Chemically Induced Magnetic Polarization" (A. R. Lepley and G. L. Closs, eds.), p. 358. Wiley, New York, 1973; T. Sasaki, K. Kanematsu, A. Kakehi, I. Ichikawa, and K. Hayakawa, *J. Org. Chem.* **35**, 426 (1970).

¹⁶⁰ J. B. Bapat, R. J. Blade, A. J. Boulton, J. Epszajn, A. R. Katritzky, J. Lewis, P. Molina-Buendia, P.-L. Nie, and C. A. Ramsden, *Tetrahedron Lett.*, 2691 (1976).

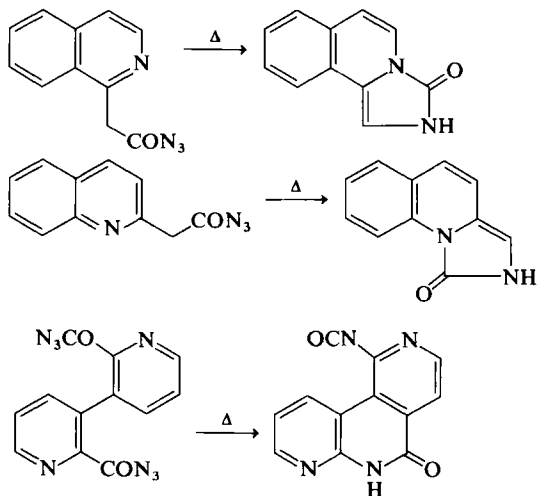
¹⁶¹ M. Iwao and T. Kuraishi, *J. Heterocycl. Chem.* **16**, 689 (1979); R. L. Williams and M. G. El Fayoumy, *ibid.* **9**, 1021 (1972).

¹⁶² M. Kurz and W. Reichen, *Tetrahedron Lett.*, 1433 (1978); R. Richter and H. Ulrich, *J. Org. Chem.* **43**, 3060 (1978).

¹⁶³ W. Reichen, *Chem. Rev.* **78**, 569 (1978).

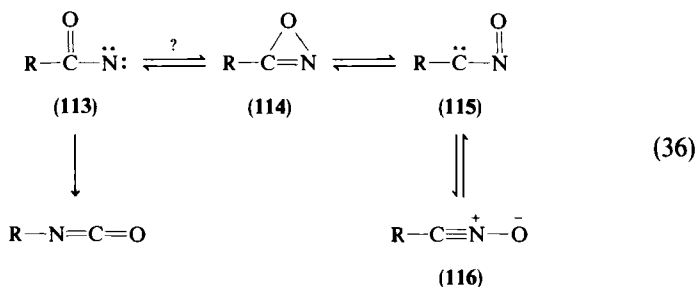


X = CH or N



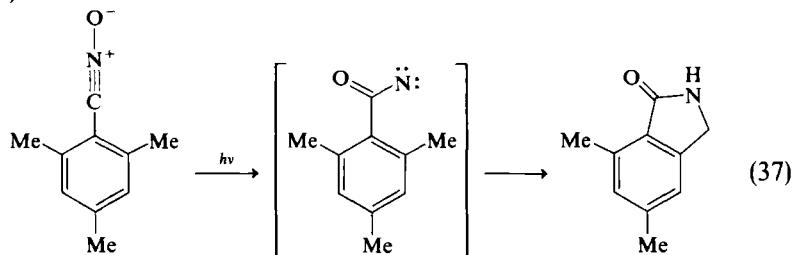
SCHEME 21

Wolff rearrangement was demonstrated. A similar reaction in an acylnitrene (113) would lead to the potentially antiaromatic oxazirine (114) (Eq. 36). By



ring opening, a nitrene-carbene rearrangement to **115** should then be possible. Compound **115** is nothing but a mesomeric or high-energy form of a nitrile oxide (**116**). Such a rearrangement has never been observed, but the reverse, the thermal or photochemical rearrangement of nitrile oxides to

isocyanates, is a well-known reaction.¹⁶⁴ The fact that nitrile oxides do rearrange thermally to isocyanates indicates that acylnitrenes (**113**) are, after all, possible isocyanate precursors. The only alternative would be a concerted rearrangement of **114** to isocyanate. *Ab initio* calculations indicate that singlet **114** ($R = H$) is not a true energy minimum, and that **113** ($R = H$) isomerizes to HNCO with an activation energy of only about 4 kcal/mol.¹⁶⁵⁻¹⁶⁷ This small barrier explains why the nitrene-carbene rearrangement **113** \rightarrow **115** has not been observed, and would seem also to be consistent with the failure to trap (singlet) acylnitrenes in thermal reactions leading to isocyanates. The question remains as to the nature of the (singlet) species which *can* be trapped in photochemical reactions, and which does not give any isocyanate. Such a species is also formed by photolysis of nitrile oxides (Eq. 37).¹⁶⁸



A reasonable explanation of all the experimental data would be that singlet nitrenes are in fact formed in thermal reactions, but they rearrange extremely rapidly to isocyanates. The intermediates which give C—H insertion products in photochemical reactions must then be excited states of the azides or, when the starting material is not an azide, an excited state of the nitrene itself [e.g., in Eqs. (33), (34), and (37)].*

The relative stabilities of nitrenes and three-membered heterocyclic rings seem to be reversed in the sulfur series: Holm and co-workers found 3-phenylthiazirine (**117**) as a stable intermediate in the photolysis of several

* Apparently, benzoylnitrene is formed in the thermolysis (120°C) of *O,N*-bis(trimethylsilyl)benzocarbimidic acid and trapped with cyclohexene to give *N*-(3-cyclohexenyl)benzamide (10%) together with phenyl isocyanate.^{168a} Benzoylnitrene is apparently also formed by sulfilimine photolysis and trapped with cyclohexene to give *N*-benzoyl-7-azabicyclo[4.1.0]heptane (15.6%).^{155a}

¹⁶⁴ J. A. Chapman, J. Crosby, C. A. Cummings, R. A. C. Rennie, and R. M. Paton, *Chem. Commun.*, 240 (1976); C. Grundmann and S. K. Datta, *J. Org. Chem.* **34**, 2016 (1969); C. Grundmann, P. Kochs, and J. R. Boal, *Justus Liebigs Ann. Chem.* **761**, 162 (1972).

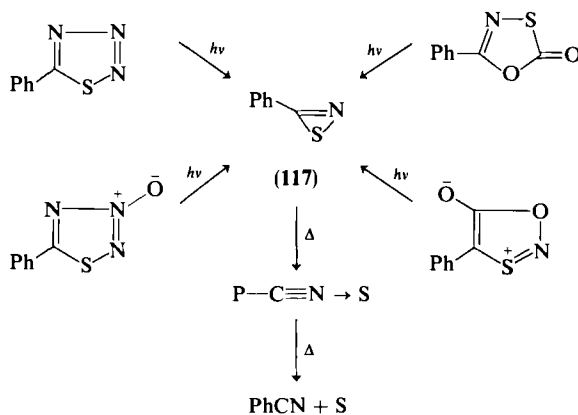
¹⁶⁵ D. Poppinger, L. Radom, and J. A. Pople, *J. Am. Chem. Soc.* **99**, 7806 (1977).

¹⁶⁶ A. Rauk and P. F. Alewood, *Can. J. Chem.* **55**, 1498 (1977).

¹⁶⁷ D. Poppinger and L. Radom, *J. Am. Chem. Soc.* **100**, 3674 (1978).

¹⁶⁸ G. Just and W. Zehetner, *Tetrahedron Lett.*, 3389 (1967).

^{168a} J. Rigaudy, E. Lytwyn, P. Wallach, and N. K. Cuong, *Tetrahedron Lett.* **21**, 3367 (1980).



SCHEME 22

heterocycles (Scheme 22) at 10–15 K,¹⁶⁹ but no evidence for the initial formation of thioacylnitrenes was obtainable.¹⁷⁰ 117 rearranged to benzonitrile sulfide on warming above 20 K, and at higher temperatures (220 K) lost sulfur, giving benzonitrile (Scheme 22).^{171,172}

VII. Imidoynitrenes and Nitrilimines (Azocarbenes)

A. ACYCLIC NITRENES

Imidoynitrenes are aza analogs of both vinylnitrenes and acylnitrenes. Not unexpectedly, therefore, the two major reactions are cyclization onto aromatic rings, forming benzimidazoles, and a Wolff-type rearrangement to carbodiimides. 1,5-Diphenyltetrazole (118) forms a mixture of 2-phenylbenzimidazole (119) (23%) and diphenylcarbodiimide (120) (76%) on thermolysis above 200°C.^{173,174} However, only the benzimidazole was formed by photolysis.¹⁷⁵

¹⁶⁹ A. Holm, N. Harrit, and I. Trabjerg, *J. C. S. Perkin I*, 746 (1978).

¹⁷⁰ A. Holm, L. Carlsen, and E. Larsen, *J. Org. Chem.* **43**, 4816 (1978).

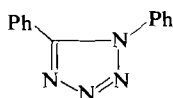
¹⁷¹ A. Holm, J. J. Christiansen, and C. Lohse, *J. C. S. Perkin I*, 960 (1976); A. Holm and N. H. Toubro, *ibid.*, 1445 (1978); cf. R. K. Hove, T. A. Gruner, L. G. Carter, L. L. Black, and J. E. Franz, *J. Org. Chem.* **43**, 3736 (1978); R. K. Hove and J. E. Franz, *ibid.*, 3742.

¹⁷² A. Holm, *Adv. Heterocycl. Chem.* **20**, 145 (1976).

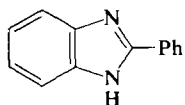
¹⁷³ P. A. S. Smith and E. Leon, *J. Am. Chem. Soc.* **80**, 4647 (1958); J. Vaughan and P. A. S. Smith, *J. Org. Chem.* **23**, 1909 (1958).

¹⁷⁴ P. A. S. Smith, in "Nitrenes" (W. Lwowski, ed.), Chapter 4. Wiley (Interscience), New York, 1970.

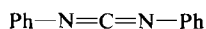
¹⁷⁵ R. M. Moriarty and J. M. Kliegman, *J. Am. Chem. Soc.* **89**, 5959 (1967).



(118)

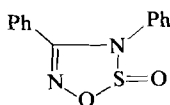


(119)

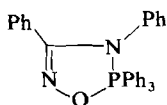


(120)

The related compounds **121**¹⁷⁶ and **122**¹⁷⁷ gave only the carbodiimide **120** on thermolysis, but a 3% yield of the benzimidazole **119** together with 62% of **120** was obtained by photolysis of **121**.^{176,178}

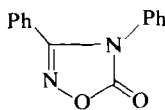


(121)

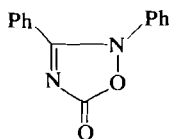


(122)

In contrast, the oxadiazolones **123** and **124** gave only benzimidazole (**119**) on thermolysis,^{179,180} whereas an additional 2% yield of the carbodiimide was formed photolytically in each case.^{180,181}



(123)



(124)

The differences observed are probably to some extent due to different reaction conditions. A more systematic study by Rees and co-workers shows that variously substituted sulfilimines (e.g., **125**), tetrazoles (**128**), and oxadiazolones (**131**) give both carbodiimides (**126**) and benzimidazoles (**129** and **130**) together with the interesting cyclopenta[*d*]pyrimidines **127** on flash vacuum pyrolysis.^{182,183} Compounds **126** and **127** were also obtained by photolysis of **125** and **128** (Scheme 23). The formation of all the products can be rationalized with the aid of a common intermediate, the imido-yl-nitrene **132** (Scheme 24) which either isomerizes to the carbodiimide or

¹⁷⁶ R. Rajagopalan and B. G. Advani, *J. Org. Chem.* **30**, 3369 (1965); A. Dondoni, G. Barbaro, and A. Battaglia, *ibid.* **42**, 3372 (1977).

¹⁷⁷ R. Huisgen and J. Wulff, *Tetrahedron Lett.*, 921 (1967).

¹⁷⁸ J. Sauer and K. K. Mayer, *Tetrahedron Lett.*, 325 (1968).

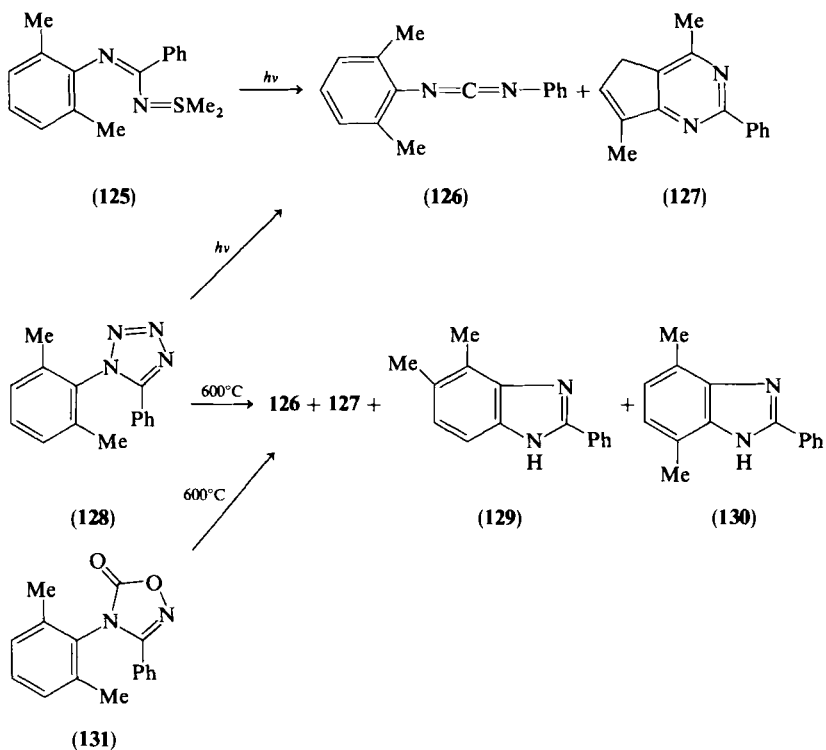
¹⁷⁹ T. Bacchetti and A. Alemagna, *Atti Accad. Naz. Lincei, Cl. Sci. Fis., Mat. Nat., Rend.* **22**, 637 (1957) [*CA* **52**, 15511 (1958)].

¹⁸⁰ J. H. Boyer and P. S. Ellis, *J. C. S. Perkin I*, 483 (1979).

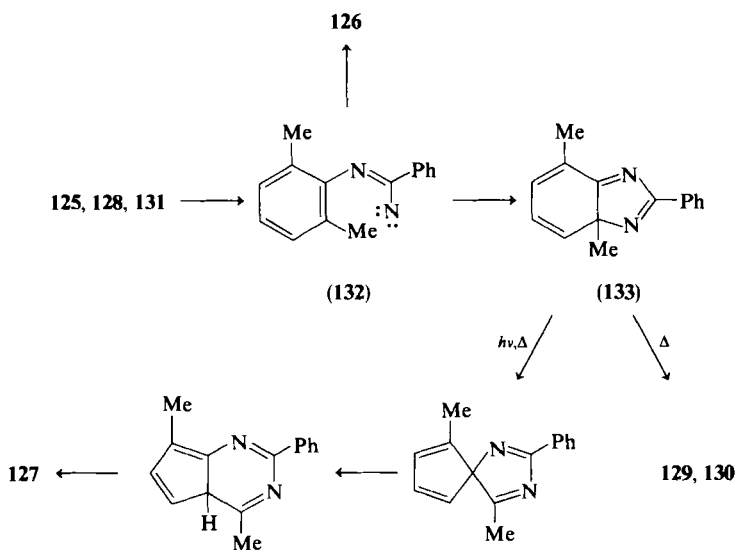
¹⁸¹ J. H. Boyer and P. J. A. Frints, *J. Heterocycl. Chem.* **7**, 59, 71 (1970).

¹⁸² T. L. Gilchrist, C. J. Moody, and C. W. Rees, *J. C. S. Perkin I*, 1964 (1975).

¹⁸³ T. L. Gilchrist, C. J. Moody, and C. W. Rees, *J. C. S. Perkin I*, 1871 (1979).



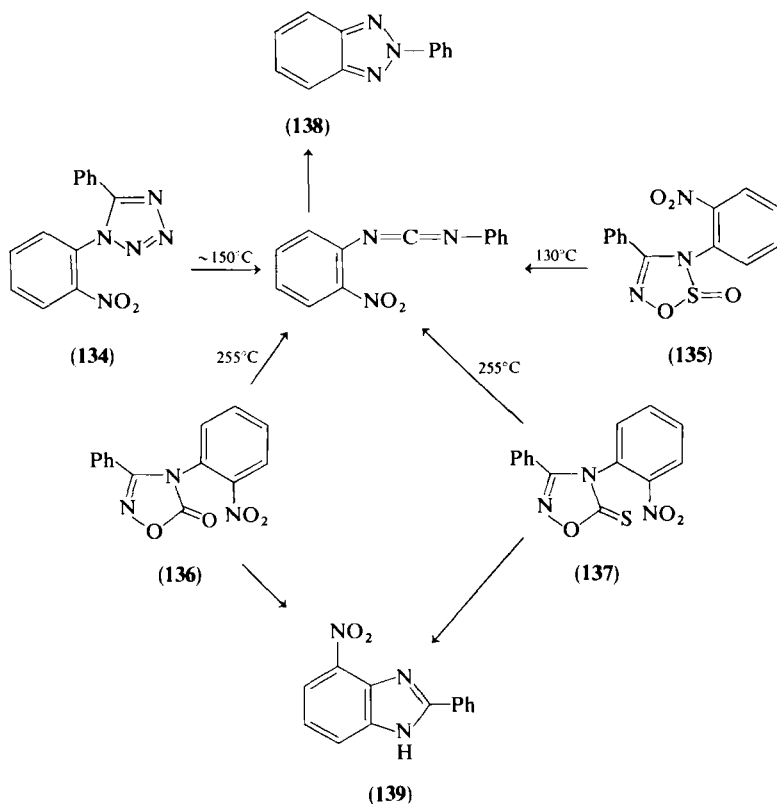
SCHEME 23



SCHEME 24

cyclizes to the transient 3a*H*-benzimidazole **133**. Several other examples of such reactions have been described.^{183,184}

Further studies showed that, when an *o*-nitro group is present, the carbodiimides formed by liquid-phase thermolysis of the heterocycles **134**–**137** underwent a novel rearrangement to 2-arylbenzotriazoles (**138**).¹⁸⁵ The yield of the latter was almost quantitative starting from **134** or **135**, but the benzimidazole **139** was the main product from **136** and **137** (Scheme 25).



SCHEME 25

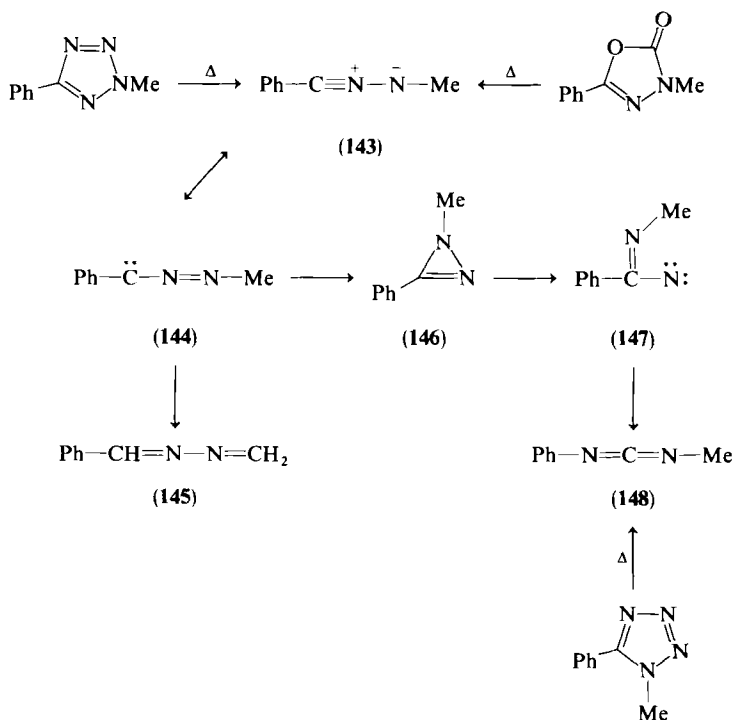
Photolysis of 1-phenyl-5-phenoxytetrazole results in nitrogen loss and cyclization to 2-phenoxybenzimidazole; the intermediate imidoynitrene could be trapped with isopropanol (Eq. 38).¹⁸⁶

¹⁸⁴ C. W. Rees, *Pure Appl. Chem.* **51**, 1243 (1979); T. L. Gilchrist, P. F. Gordon, D. F. Pipe, and C. W. Rees, *J. C. S. Perkin I*, 2303 (1979).

¹⁸⁵ P. G. Houghton, D. F. Pipe, and C. W. Rees, *Chem. Commun.*, 771 (1979).

¹⁸⁶ F. L. Bach, J. Karliner, and G. E. van Lear, *Chem. Commun.*, 1110 (1969).

This scheme suggests that an interconversion between imidoynitrenes, diazirines, and nitrilimines might be possible. This would be completely analogous to the vinylnitrene-2*H*-azirine-nitrile ylide rearrangement (Section II) and the Wolff-type rearrangements described in Sections III-IV. Evidence for such an interconversion has been obtained¹⁹⁰: flash vacuum pyrolysis of both 2-methyl-5-phenyltetrazole and 3-methyl-5-phenyl-1,3,4-oxadiazol-2(3*H*)-one gave an intermediate nitrilimine (143) which, in keeping with the calculations of Caramella and Houk,⁴⁵ can also be formulated as the azocarbene 144. A 1,4-hydrogen shift in 144 gave the isolated azine 145. In addition, the carbodiimide 148 was isolated in both cases, thereby supporting the postulated rearrangement 144 → 146 → 147. The unstable phenylmethylcarbodiimide 148 was isolated in quantitative yield at low temperature, following the flash vacuum pyrolysis of 1-methyl-5-phenyl-tetrazole. Other mixed alkylphenylcarbodiimides can be prepared similarly (Scheme 28).¹⁹⁰ It is well known that nitrilimines such as 143, formed



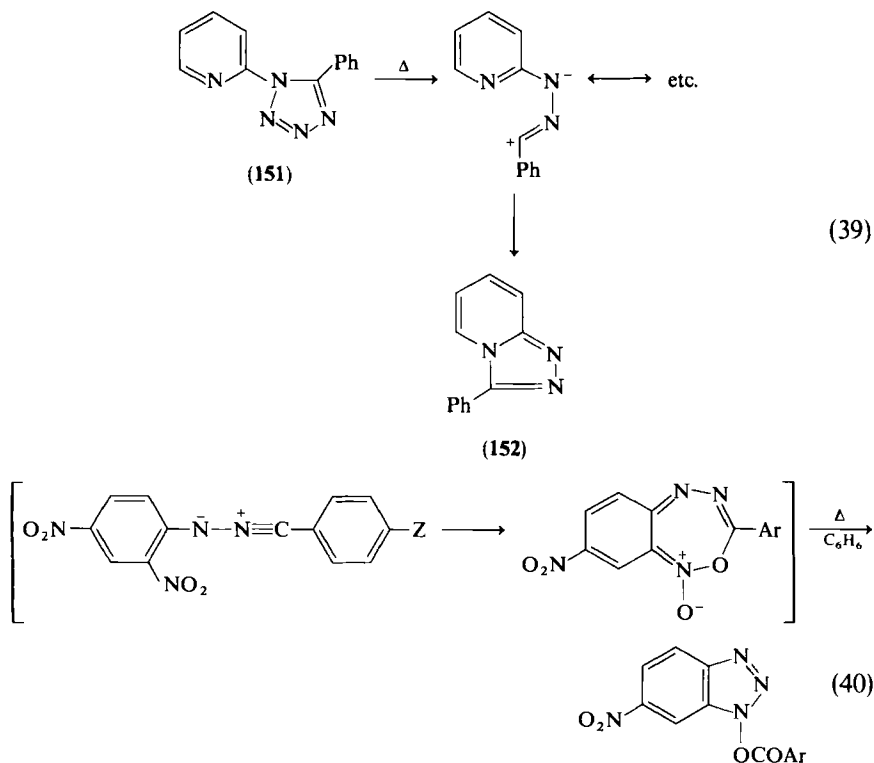
SCHEME 28

¹⁹⁰ S. Fischer, Dipl.-Chem. Thesis, University of Marburg (1979); S. Fischer and C. Wentrup, *Chem. Commun.*, 502 (1980).

The relative energies of 1*H*-diazirine, nitrilimine (HCNNH), 3*H*-diazirine, diazomethane, isocyanamide (H₂NNC), carbodiimide (HNCNH), and cyanamide were calculated with an STO-6-31G basis set to decrease in the order given.¹⁹²

A rearrangement of the type shown in Scheme 28 cannot be observed with *C,N*-diphenylnitrilimines, because these cyclize onto the aromatic ring bound to N, giving indazoles (Scheme 29). The reaction is virtually quantitative and therefore of synthetic value for the preparation of 3-arylidazoles and pyrazolopyridines (**149**).^{193,194} When the same reaction is carried out at 800°C (flash pyrolysis), a further molecule of N₂ is extruded, giving a new carbene which cyclizes to fluorenes or azafluorenes (**150**), again in quantitative yields (Scheme 29).¹⁹³

Nitrilimines (azocarbenes) generated from 2-(2-azinyl)-5-phenyltetrazoles (e.g., **151**) cyclize onto nitrogen, giving 1,2,4-triazoloazines (e.g., **152**) (Eq. 39).¹⁹⁵



¹⁹² J. B. Moffat, *J. Mol. Struct.* **52**, 275 (1979).

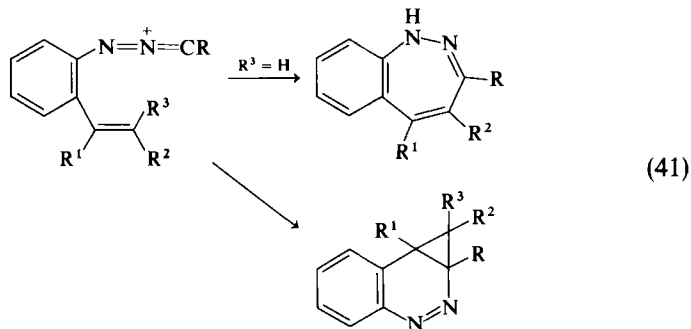
¹⁹³ C. Wentrup, A. Damerius, and W. Reichen, *J. Org. Chem.* **43**, 2037 (1978).

¹⁹⁴ C. Wentrup and J. Benedikt, *J. Org. Chem.* **45**, 1407 (1980).

¹⁹⁵ A. Könnecke and E. Lippmann, *Z. Chem.* **18**, 175 (1978).

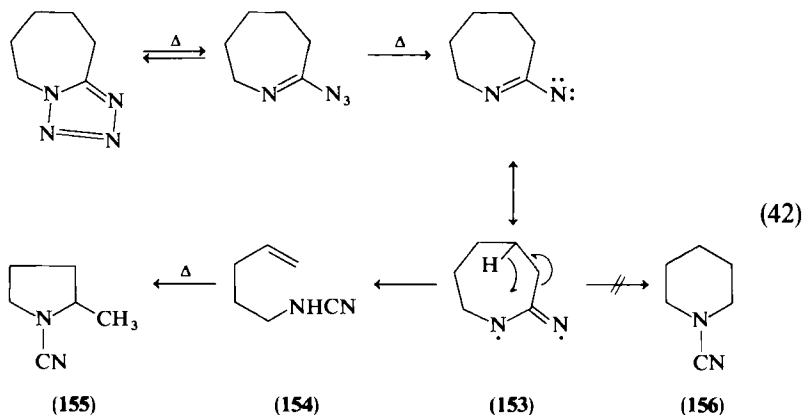
Similarly generated diarylnitrilimines carrying *o*-nitro groups rearrange thermally to benzotriazoles (Eq. 40).¹⁹⁶

In analogy with the carbenoid 1,1-cyloadditions of nitrile ylides (Section II,B), nitrilimines can undergo intramolecular cyclizations to give 1,2-diazepines or cyclopropa[*c*]cinnolines (Eq. 41).¹⁹⁷ The latter compounds are formed stereospecifically, thus supporting a concerted carbene-like 1,1-addition of the nitrilimine to the olefinic double bond.^{197a}



B. SEMICYCLIC IMIDOYLNITRENES

Imidoynitrenes that are part of an aromatic system are treated in Section VIII. Nonaromatic semicyclic imidoynitrenes have been generated by flash vacuum pyrolysis of 1,5-polymethylenetetrazoles and were found to undergo



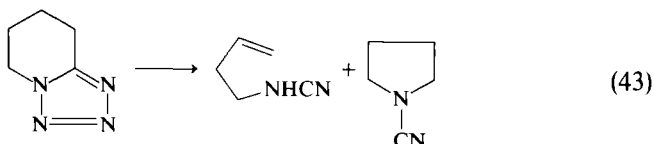
¹⁹⁶ A. Könnecke, P. Lepom, and E. Lippmann, *Z. Chem.* **18**, 214 (1978).

¹⁹⁷ L. Garanti and G. Zecchi, *J. C. S. Perkin I*, 2092 (1977); L. Chiodini, L. Garanti, and G. Zecchi, *Synthesis*, 603 (1978).

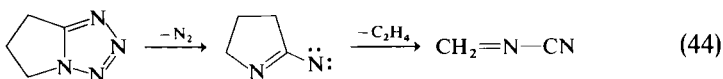
^{197a} A. Padwa and S. Nahm, *J. Org. Chem.* **44**, 4746 (1979).

ring opening and recyclization.¹⁹⁸ Thus, pentamethylenetetrazole gave 4-pentenylcyanamide (**154**) and 1-cyano-2-methylpyrrolidine (**155**) (Eq. 42). The absence of 1-cyanopiperidine (**156**) and the fact that **154** isomerizes to **155** under mild conditions indicate the stepwise process shown (a concerted rearrangement of **153** to **154** is not implied).

Similarly, tetramethylenetetrazole gave a mixture of 3-butenylcyanamide and 1-cyanopyrrolidine (Eq. 43).¹⁹⁸



Trimethylenetetrazole gave as the main products nitrogen, ethylene, and poly-*N*-cyanoformimine. The monomer $\text{CH}_2=\text{N}-\text{CN}$ could be detected by direct introduction of the pyrolysis vapors into a mass spectrometer (Eq. 44)¹⁹⁸ and has been fully identified by millimeter wave spectroscopy.^{198a}



VIII. Arylcarbenes and Arylnitrenes

Having presented the simple, open-chain unsaturated carbenes and nitrenes, we can now discuss the more complicated aromatic systems.

A. MECHANISM OF CARBENE-NITRENE REARRANGEMENTS

The mechanisms of the rearrangements and interconversions of arylcarbenes and arylnitrenes have been reviewed in considerable detail.^{10,13,14} It is the purpose of this section to summarize the most important findings and to update the previous reviews.

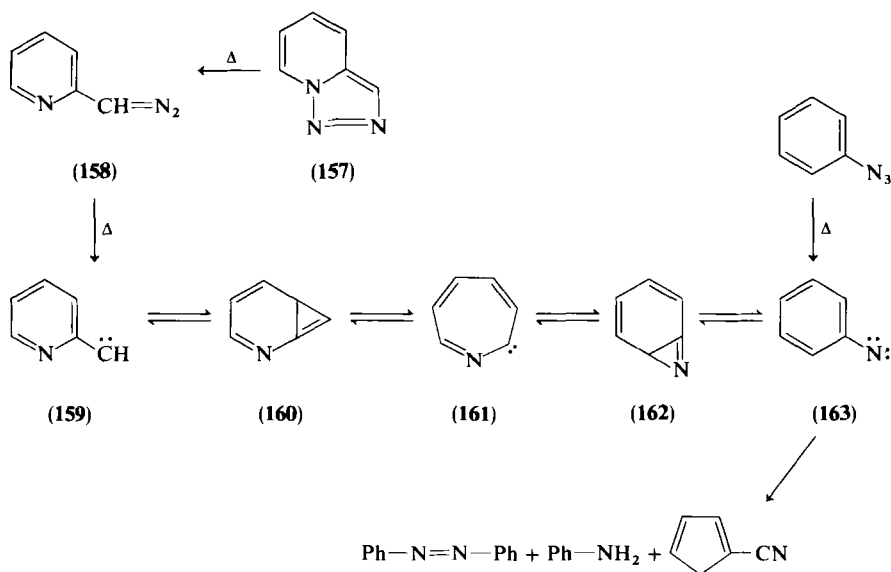
Phenylnitrene and 2-pyridylcarbene interconvert in the gas phase, as evidenced by the formation of identical products from phenyl azides and 2-(diazomethyl)pyridines (Scheme 30).^{199,200} Although the carbene precursor **157** exists as a triazole in the solid state, the diazomethane valence tautomer

¹⁹⁸ C. Wentrup, *Tetrahedron* **27**, 1281 (1971).

^{198a} M. Winnewisser, B. P. Winnewisser, and C. Wentrup, unpublished results.

¹⁹⁹ W. D. Crow and C. Wentrup, *Tetrahedron Lett.*, 6149 (1968).

²⁰⁰ C. Wentrup, *Chem. Commun.*, 1386 (1969).



SCHEME 30

158 can be trapped in solution.¹⁸⁸ Furthermore, 2-(diazomethyl)pyridine (**158**) can be isolated and identified by its IR spectrum by subliming **157** through a tube at 100°C (10⁻³ torr) and condensing the vapors on a KBr disk at -196°C.¹⁸⁹ Similar results were obtained with other triazoloazines, so that it is fairly certain that diazomethylazines are the immediate carbene precursors in the gas phase. Since also 5-aryltetrazoles decompose to aryl-diazomethanes in the gas phase (Scheme 27), 5-(2-pyridyl)tetrazole may be used as a precursor of **158**.^{201,202} Evidence that the rearrangement **159** → **163** occurs *formally* through the atomic movements represented by the formulae **160**, **161**, and **162** was secured from the nature of the azobenzenes, anilines, or carbazoles formed from substituted starting materials,^{199,200} and by ¹³C-labeling of 2-pyridylcarbene (Scheme 31). The azobenzene isolated was found to be exclusively labeled in the ortho positions.^{203 *}

Crow *et al.*^{201,204} found that also 3- and 4-pyridylcarbenes are converted to phenylnitrene. A ¹³C-labeling study of 4-pyridylcarbene by Thétaz

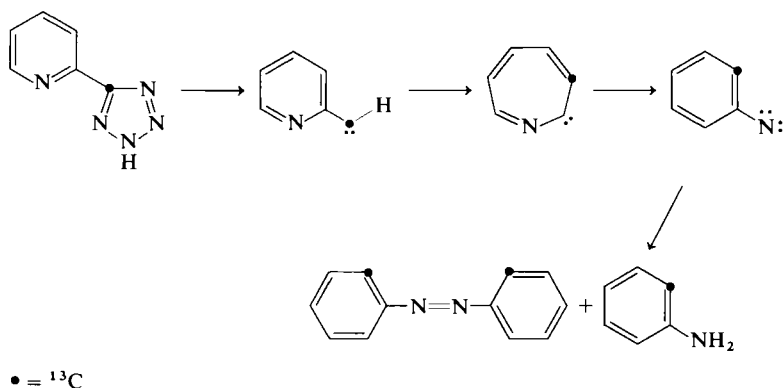
* The formation of seven-membered ring intermediates has been ascertained by the isolation of a dimer, perfluoro-2,7'-diazahptafulvalene, from the pyrolysis of azidopentafluorobenzene [R. E. Banks, N. D. Venayak, and T. A. Hamor, *Chem. Commun.*, 900 (1980)].

²⁰¹ W. D. Crow, M. N. Paddon-Row, and D. S. Sutherland, *Tetrahedron Lett.*, 2239 (1972).

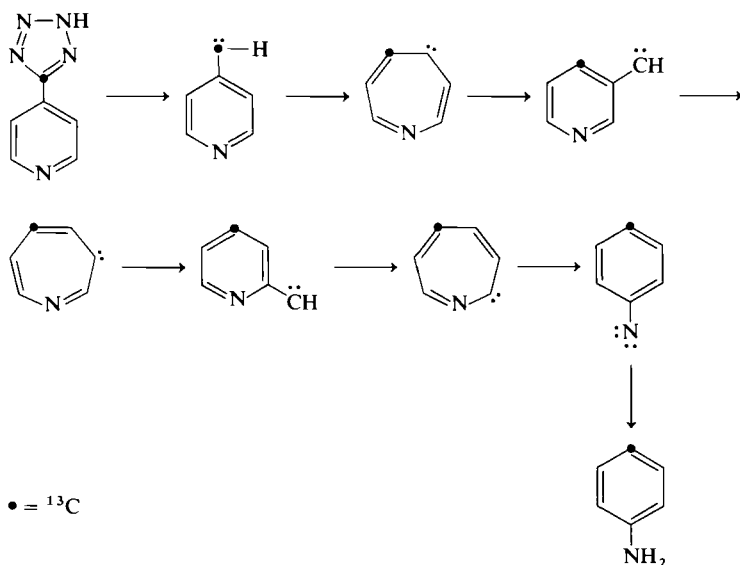
²⁰² C. Wentrup, C. Mayor, and R. Gleiter, *Helv. Chim. Acta* **55**, 2628 (1972); erratum, 3066.

²⁰³ C. Thétaz and C. Wentrup, *J. Am. Chem. Soc.* **98**, 1258 (1976).

²⁰⁴ W. D. Crow, A. N. Khan, and M. N. Paddon-Row, *Aust. J. Chem.* **28**, 1741 (1975).



SCHEME 31



SCHEME 32

et al.^{203,205} showed that the aniline formed (from phenylnitrene by hydrogen abstraction) was exclusively labeled in the para position in agreement with the mechanism shown in Scheme 32. Less than 1.5% ^{13}C was detectable in the ortho and meta positions (natural abundance: 1.1%).²⁰⁵

Although the gross features of the rearrangements are known, the exact nature of the intermediates has been the subject of much discussion. They are presented above as azacycloheptatrienylidenes (e.g., **161**) in analogy with the

²⁰⁵ C. Thétaz, Ph.D. Thesis, University of Lausanne (1977).

rearrangement of phenylcarbene to cycloheptatrienyldiene.^{10,13,14,206-209} However, it has been recognized for many years that also azacycloheptatetraene structures (e.g., **164**) may play a role.^{10,13,210,211}



(164)

Although semiempirical calculations²¹¹ discarded **164** as an intermediate, other calculations^{212,213} on the all-carbon analogs favored 1,2,4,6-cycloheptatetraene in equilibrium with—or to the exclusion of—cycloheptatrienyldiene. Furthermore, evidence that cycloheptatetraene can be generated in solution has been published.^{214,215}

Another mechanistic problem concerned the involvement of the bicyclic intermediates, **160** and **162** (Scheme 30). Compound **162** has been postulated for many years²¹⁶ as the intermediate which is trapped by nucleophiles in the thermolysis or photolysis of aryl azides, leading to azepines (this reaction is described in detail in Section VIII,C). However, the present author pointed out that there was no compelling evidence for **162**, and that the trappable intermediate could equally well be the seven-membered ring **161**.²¹⁷ The question then arises: is **163** → **161** a one-step reaction, or does it take place via **162**? (see Scheme 30). CNDO/2 and extended Hückel calculation failed to answer this question unambiguously, but both methods showed that the nitrene N in **163** must move out of the plane of the ring *en route* to **161**.²¹⁸ The calculations by Shillady and Trindle²¹¹ favored **162** as a stable intermediate. There is no doubt of the existence of carbocyclic analogs of **162**, which can be trapped^{219,220} in solution [e.g., Eq. (45)].²¹⁹

²⁰⁶ R. C. Joines, A. B. Turner, and W. M. Jones, *J. Am. Chem. Soc.* **91**, 7754 (1969).

²⁰⁷ P. Schissel, M. E. Kent, D. J. McAdoo, and E. Hedaya, *J. Am. Chem. Soc.* **92**, 2147 (1970).

²⁰⁸ C. Wentrup and K. Wilczek, *Helv. Chim. Acta* **53**, 1459 (1970).

²⁰⁹ W. M. Jones and U. H. Brinker, in "Pericyclic Reactions" (A. P. Marchand and R. E. Lehr, eds.), Vol. I, p. 109. Academic Press, New York, 1977.

²¹⁰ N. M. Lân and C. Wentrup, *Helv. Chim. Acta* **59**, 2068 (1976).

²¹¹ D. D. Shillady and C. Trindle, *Theor. Chim. Acta* **43**, 137 (1976).

²¹² R. L. Tyner, W. M. Jones, Y. Öhrn, and J. R. Sabin, *J. Am. Chem. Soc.* **96**, 3765 (1974).

²¹³ M. J. S. Dewar and D. Landman, *J. Am. Chem. Soc.* **99**, 6179 (1977).

²¹⁴ C. Mayor and W. M. Jones, *Tetrahedron Lett.*, 3855 (1977); *J. Org. Chem.* **43**, 4498 (1978).

²¹⁵ W. M. Jones, *Acc. Chem. Res.* **10**, 353 (1977).

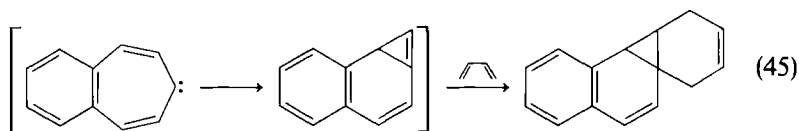
²¹⁶ R. Huisgen, *Angew. Chem.* **67**, 756 (1955); R. Huisgen, D. Vossius, and M. Appl, *Chem. Ber.* **91**, 1 (1958).

²¹⁷ C. Wentrup, *Tetrahedron* **30**, 1301 (1974).

²¹⁸ R. Gleiter, W. Rettig, and C. Wentrup, *Helv. Chim. Acta* **57**, 2111 (1974).

²¹⁹ T. T. Coburn and W. M. Jones, *J. Am. Chem. Soc.* **96**, 5218 (1974).

²²⁰ W. E. Billups, L. P. Lin, and W. Y. Chow, *J. Am. Chem. Soc.* **96**, 4026 (1974).



Evidence for the formation of azirines of the type **162** by matrix photolysis of aryl azides is also beginning to appear.^{220a} In some cases it can be ascertained, however, that the seven-membered ring intermediates are more stable than the fused bicyclic azirines. Furthermore, in all cases uncovered to date it turns out that the seven-membered rings, when isolable, exist as cumulenes rather than carbenes.

For example, 2-quinolynitrene rearranges thermally to 1-isoquinolynitrene, from which the products **166a–c** arise (Scheme 33).^{221,222,222a} The cyclic carbodiimide **165** ($R = H$) was isolable at -196°C and directly observable by IR spectroscopy (2000 cm^{-1}) following flash vacuum pyrolysis of either tetrazolo[1,5-*a*]quinoline or tetrazolo[5,1-*a*]isoquinoline at 490°C .^{222a} Compound **165** dimerized on warming to -55°C .^{222a} This intermediate had originally been postulated as the mesomeric form **165a** (Scheme 33).²²¹ The bicyclic azirines **167** and **168** (Scheme 33) can be written as intermediates or transition states *en route* to **165**, but they are not expected to be stable intermediates under these reaction conditions, and no evidence for their formation has been obtained.

In a manner formally analogous to the rearrangement shown in Scheme 33, 2-quinolylcarbene and 1-isoquinolylcarbene rearrange thermally to 1-naphthylnitrene and 2-naphthylnitrene, respectively (Scheme 34).^{202,223} 9-Phenanthridylnitrene affords the cyclic carbodiimide **169**, which can be prepared almost pure by pyrolysis at 490°C , condensing the product at -196°C . Compound **169** is stable up to about -40°C , where dimerization occurs.^{222a} In this case, the fused azirine **170** (Scheme 34) is expected to be highly unstable due to complete loss of aromaticity, and no evidence for its formation has been found.

Even more facile ring expansions are observed in the quinazolinylnitrenes **173** and **175** which rearrange to **177** and **181** already in solution (in toluene or mesitylene at 180°C in a sealed tube, or very slowly in refluxing benzene) (Scheme 35).^{205,224} Thermochemical calculations indi-

^{220a} J. I. G. Cadogan, private communication; I. R. Dunkin and P. C. P. Thomson, private communication; *Chem. Commun.*, 499 (1980).

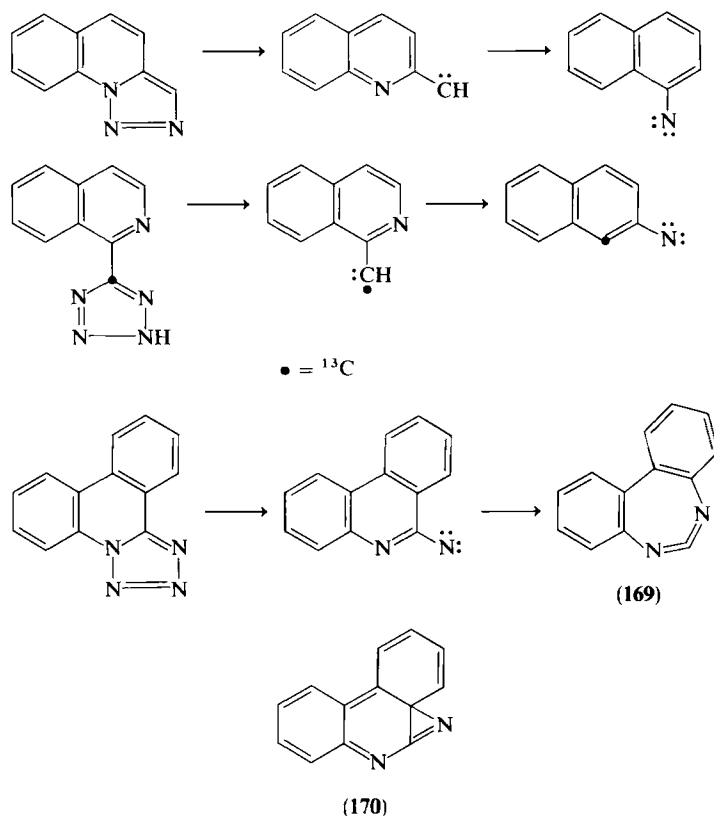
²²¹ C. Wentrup, *Tetrahedron* **27**, 367 (1971).

²²² C. Wentrup, C. Thétaz, and R. Gleiter, *Helv. Chim. Acta* **55**, 2633 (1972).

^{222a} C. Wentrup and H.-W. Winter, *J. Am. Chem. Soc.* **102**, 6159 (1980).

²²³ N. M. Lân, Ph.D. Thesis, University of Lausanne (1977).

²²⁴ E. Tagliaferri, Diploma Thesis, University of Lausanne (1976).



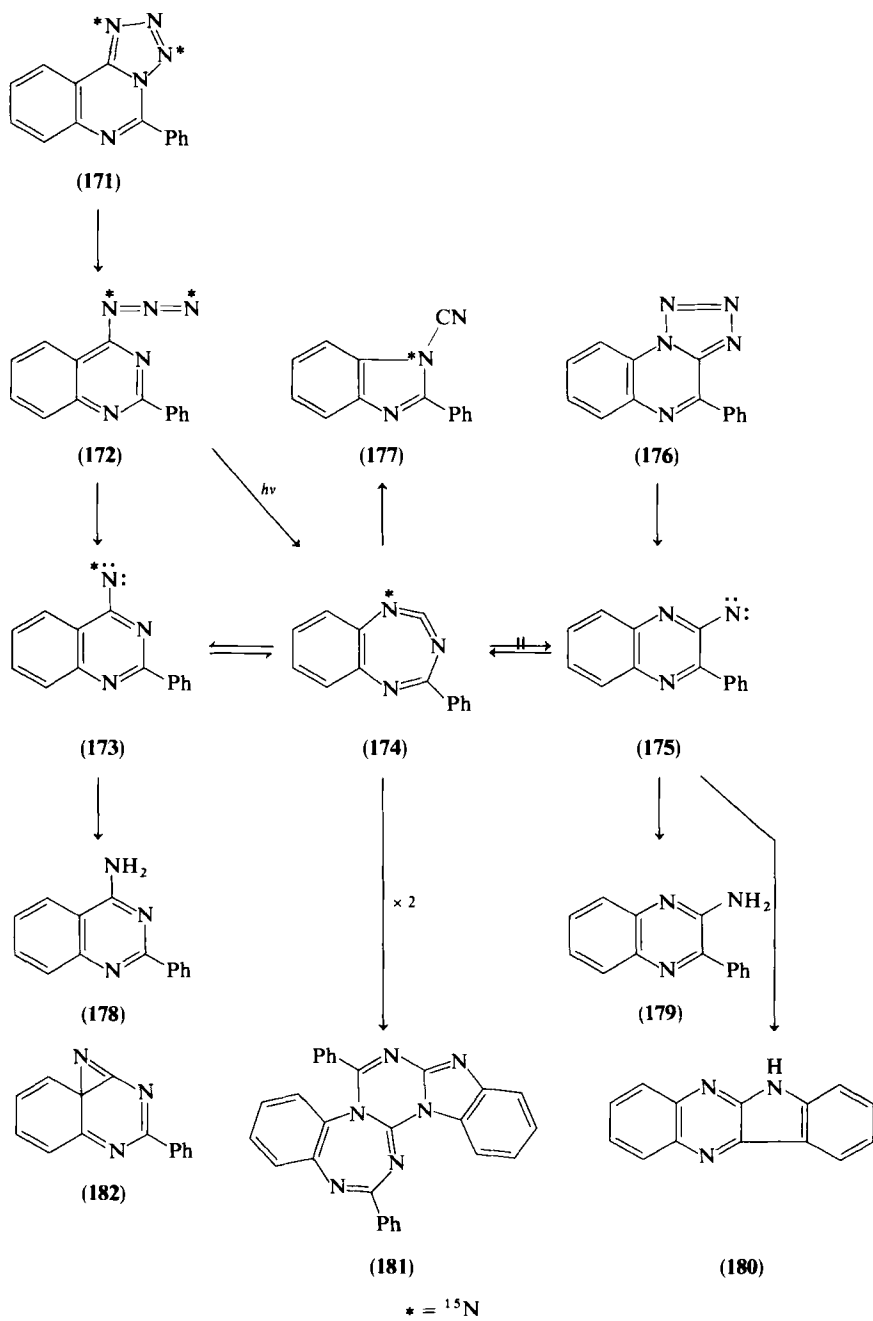
SCHEME 34

cate that the formation of the azirine **182** from the 4-quinazolylnitrene **173** would be strongly endothermic.¹⁰ The key rearrangement in Scheme 35 (**173** → **174**) is therefore considered as a one-step Wolff-type ring expansion. The intermediate **174** is considered to be a carbodiimide²²⁵ because the related carbene would have lost aromatic resonance energy, and because it dimerizes in solution. The structure of the dimer (**181**) was established by X-ray crystallography²²⁵; apparently it arises through a rearrangement of an initially formed carbodiimide dimer.

The tetrazole **171** exists as the azide **172** in the gas phase.²²⁷ Compound **172** gave a quantitative yield of the 1-cyanobenzimidazole **177** on flash vacuum pyrolysis above 300°C.^{222,226} When the nitrene N was labeled with

²²⁵ E. Tagliaferri and C. Wentrup, Communication presented at the Autumn Meeting of the Swiss Chemical Society, Berne, Oct. 8, 1977, Group D.

²²⁶ C. Wentrup and C. Thétaz, *Helv. Chim. Acta* **59**, 256 (1976).



SCHEME 35

^{15}N , the label was found *exclusively in the ring* in **177**, proving that **177** cannot arise directly from the nitrene **173**. It cannot arise from the isomeric nitrene **175** either, since one of the products of this nitrene (indoloquinoline **180**) was absent.²²² The same nitrile (**177**) was also formed by solution pyrolysis of either **171** or **176**, again with at least 78% of the label in the ring.^{13,205} The individual nitrenes (**173** and **175**) could be trapped with octanethiol in solution, giving the amines **178** and **179**, respectively. No cross-over between the amines was observed.²²⁴ From these results, the cyclic carbodiimide (**174**) is the only reasonable precursor of the products **177** and **181**.^{224,225} Finally, the carbodiimide **174** was directly observed by its IR spectrum (2010 cm^{-1}) by photolysis of the azide **172** in argon matrix at 10 K,²²⁷ but this last proof followed an exciting new development due to Chapman and co-workers (Section VIII,B).

B. MATRIX PHOTOCHEMISTRY

Chapman and LeRoux found that the photolysis of phenyl azide and 2-diazomethylpyridine in argon matrix at 8 K produced a common intermediate, 1-aza-1,2,4,6-cycloheptatetraene (**183**), which was characterized by a strong IR absorption at 1895 cm^{-1} .⁴⁹ Further photolysis destroyed **183** in an unknown manner. Monitoring the reaction with ESR spectroscopy allowed the direct observation of triplet phenylnitrene (**184**) and triplet 2-pyridylcarbene (**185**). Furthermore, these two species were interconverted photochemically, but not thermally. It may be assumed, therefore, that singlet and triplet states are in photochemical equilibrium, and that the interconversions occur on the singlet energy surface. The 4- and 3-pyridyl-carbenes were found to give a common allene **187** ($\text{IR } 1810\text{ cm}^{-1}$), and on further photolysis **183**.²²⁸ The conversion of the triplet species, $\mathbf{186} \rightleftharpoons \mathbf{188} \rightarrow \mathbf{185} \rightleftharpoons \mathbf{184}$ was observable by ESR spectroscopy (Scheme 36).²²⁸

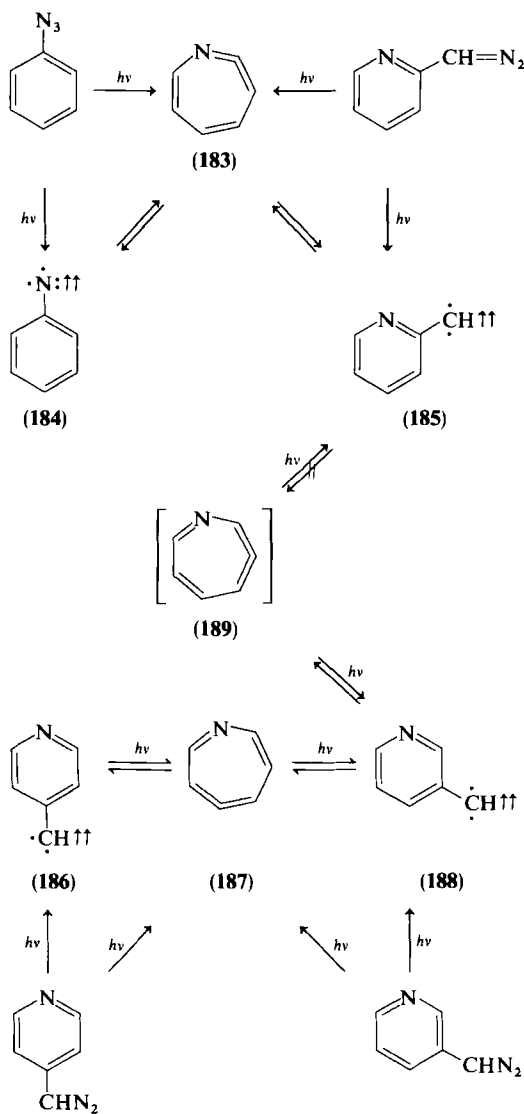
The proposed intermediate (**189**) connecting the 2- and 3-pyridylcarbenes was not observed, but in further studies^{229,230} a novel intermediate absorbing at 1935 cm^{-1} was produced on long wavelength irradiation of 3-pyridylcarbene. This intermediate was assigned the zwitterionic structure **190** and was photochemically converted to **187** and then to **183** without further intermediates being detectable by IR spectroscopy. Thus, **190** occupies the

²²⁷ C. Wentrup, C. Thétaz, E. Tagliaferri, H. J. Lindner, B. Kitschke, H.-W. Winter, and H. P. Reisenauer, *Angew. Chem., Int. Ed. Engl.* **19**, 566 (1980).

²²⁸ O. L. Chapman, R. S. Sheridan, and J.-P. LeRoux, *J. Am. Chem. Soc.* **100**, 6245 (1978).

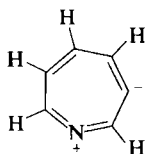
²²⁹ O. L. Chapman, R. S. Sheridan, and J.-P. LeRoux, *Recl. Trav. Chim. Pays-Bas* **98**, 334 (1979).

²³⁰ O. L. Chapman and R. S. Sheridan, *J. Am. Chem. Soc.* **101**, 3690 (1979).



SCHEME 36

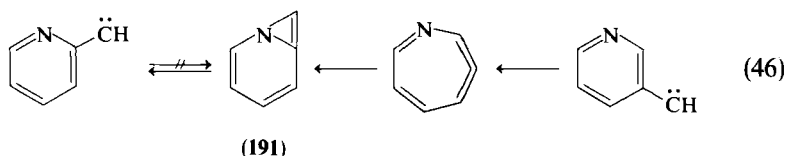
position expected for the allene **189** in Scheme 36. Since the conversion of **190** to **183** appeared to take place by way of **187**, possible mechanisms for the direct conversion **187** → **183** were considered.²²⁹ One mechanism proposed involves a movement of the central allenic carbon atom on the π -surface of pyridine, and is identical with a previous proposal for carbocyclic



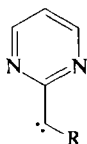
(190)

carbene-carbene rearrangements.²³¹ No evidence for this mechanism has been obtained, however.

It is noteworthy that a return of 2-pyridylcarbene (**185**) to 3- or 4-pyridylcarbene has not been observed.^{228,229} This parallels the observations from the thermal chemistry that 2-pyridylcarbene expands exclusively by "insertion" into the 2,3-bond, not into the 1,2-bond of pyridine.^{199,204,232} The nonoccurrence of this latter reaction (**185** → **189**) is due to the unfavorable nonbonded interaction between the nitrogen lone pair and the filled carbene π -orbital during such a rearrangement.^{202,232} In the extreme case, a bicyclic intermediate in this reaction would be the antiaromatic 1*H*-azirine **191** (Eq. 46). On the other hand, 3-pyridylcarbene can hardly avoid



passing through **191** (or a transition state of similar structure) *en route* to 2-pyridylcarbene. The above-mentioned rearrangement of [*p*-¹³C]pyridylcarbene to [*p*-¹³C]phenylnitrene (Scheme 32) includes such a step. That the antiaromaticity of intermediates or transition states like **191** is not a serious obstacle toward ring expansion is also shown by the fact that 2-pyrimidylcarbenes (**192**) do undergo thermal ring expansions.^{10,202,218,232}



(192) R = H or Ph

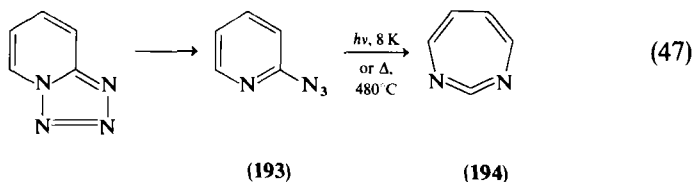
2-Pyridyl azide (**193**) can be prepared by mild pyrolysis^{222a} or photolysis²³³ of tetrazolo[1,5-*a*]pyridine. Pyrolysis at 480°C^{222a} or photolysis in argon

²³¹ W. J. Baron, M. Jones, and P. P. Gaspar, *J. Am. Chem. Soc.* **92**, 4739 (1970).

²³² C. Mayor and C. Wentrup, *J. Am. Chem. Soc.* **97**, 7467 (1975).

²³³ O. L. Chapman, *Pure Appl. Chem.* **51**, 331 (1979).

matrix at 8 K²³³ affords the cyclic carbodiimide **194** which is stable to about -70°C and absorbs at 1975 cm^{-1} in the IR^{222a} (Eq. 47).

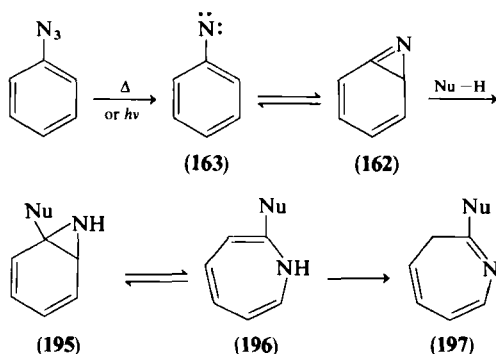


C. FORMATION OF AZEPINES AND *o*-DIAMINES

1. From Azides

Huisgen²¹⁶ was the first to establish the formation of azepines by thermolysis of aryl azides in aniline, a reaction first investigated by Wolff in 1912.²³⁴ Doering and Odum²³⁵ found that the same reaction can be achieved photolytically. The key intermediate in the Huisgen–Doering mechanism is the bicyclic azirine **162** (Scheme 37) which was thought to be trapped by the nucleophile (Nu = aniline) to give the 7-azanorcaradiene **195**. Valence tautomerization to **196** followed by a hydrogen shift gives the final 3*H*-azepine (**197**). Abramovitch² suggested that the step $\mathbf{163} \rightleftharpoons \mathbf{162}$ is reversible.

Sundberg showed that 1*H*-azepines (**196**) are indeed formed initially during photolysis of aryl azides in diethylamine (Nu = Et₂N).²³⁶ Early



SCHEME 37

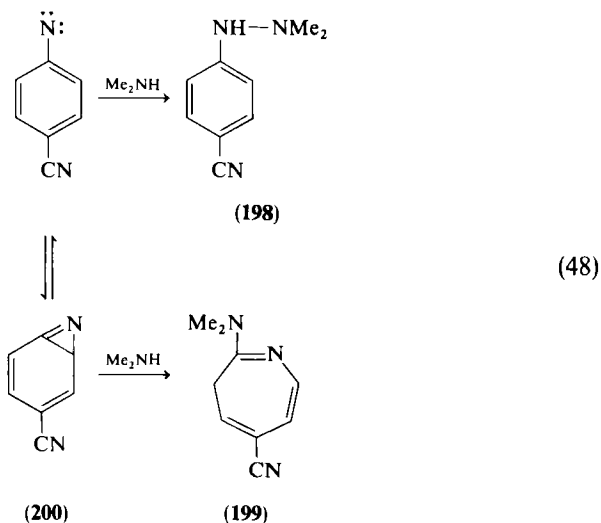
²³⁴ L. Wolff, *Justus Liebigs Ann. Chem.* **394**, 59 (1912).

²³⁵ W. von E. Doering and R. A. Odum, *Tetrahedron* **22**, 81 (1966).

²³⁶ R. J. Sundberg, S. R. Suter, and M. Brenner, *J. Am. Chem. Soc.* **94**, 513 (1972).

evidence that the trappable intermediate cannot be phenylnitrene (**163**) itself has been summarized.^{1,2,7,174} Splitter and Calvin showed that it is the singlet phenylnitrene which undergoes the rearrangement: triplet sensitization with *p*-dimethylaminobenzaldehyde caused a drop in the yield of azepine, giving instead aniline, the latter being derived from the triplet nitrene. In the unsensitized photolysis, azepine formation was not inhibited by oxygen, a triplet quencher.²³⁷

Odum and Wolf found that the yields of the two competitive photo-reactions of *p*-cyanophenylnitrene (Eq. 48) were dependent on the wavelength of the irradiating light: higher energy light increased the yield of the azepine.²³⁸ Furthermore at each wavelength, the ratio of **198** to **199** decreased as the concentration of dimethylamine decreased. Since both products arise from the singlet nitrene,^{237,239} the data required at least one intermediate different from the nitrene. This was thought to be the azirine **200**.²³⁸



DeGraff, Gillespie, and Sundberg reported a flash photolytic investigation of the reaction of phenylnitrene and ortho-substituted derivatives with dibutylamine.²⁴⁰ An intermediate was observed which did not absorb beyond 300 nm, and which was trapped by the amine over a period of about 300 μsec

²³⁷ J. S. Splitter and M. Calvin, *Tetrahedron Lett.*, 1445 (1968).

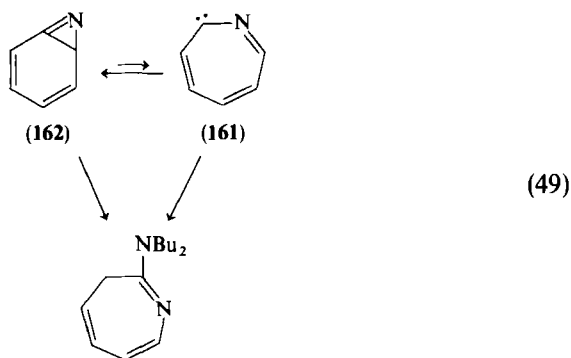
²³⁸ R. A. Odum and G. Wolf, *Chem. Commun.*, 360 (1973).

²³⁹ R. A. Odum and A. M. Aaronson, *J. Am. Chem. Soc.* **91**, 5680 (1969).

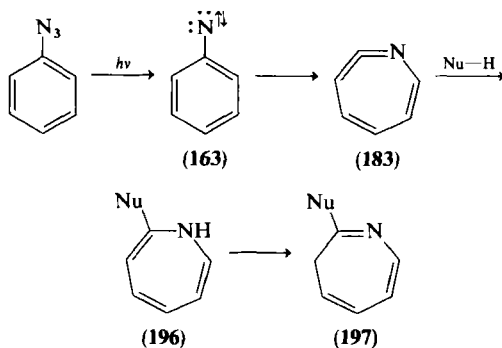
²⁴⁰ B. A. DeGraff, D. W. Gillespie, and R. J. Sundberg, *J. Am. Chem. Soc.* **96**, 7491 (1974).

with rates in the range 10^4 – 10^9 liter mol^{-1} sec^{-1} . The half-life of the intermediate in the absence of trapping agent was estimated as about 5 msec. Since an upper limit of about 30 μsec was placed on the life-time of phenyl-nitrene, and since the latter was expected to absorb above 300 nm, it was rejected as a candidate for the observable intermediate. Again, the azirine **162** was favored, and this was supported by semiempirical calculations.²¹¹ As mentioned above, Wentrup suggested that azacycloheptatrienyldiene (**161**) rather than the azirine **162** was the intermediate in all these reactions.^{10,217}

DeGraff *et al.* did not entirely discard the possible seven-membered $\text{C}_6\text{H}_5\text{N}$ intermediates **161** and **183**. Indeed, the observation of a negative energy of activation for the trapping of the intermediate from phenyl azide led to the postulate that two $\text{C}_6\text{H}_5\text{N}$ species are in rapid equilibrium, with the thermodynamically more stable species being more reactive toward dibutylamine. The favored intermediates are shown in Eq. (49).²⁴⁰



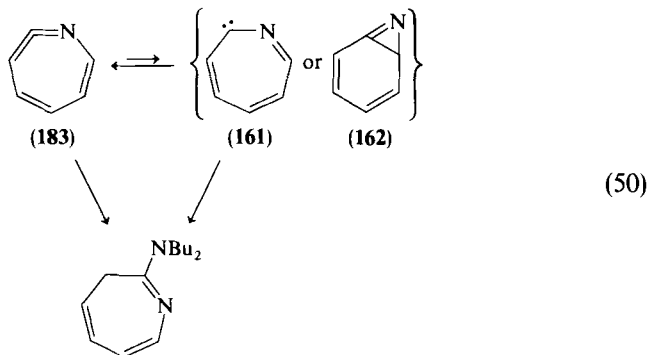
Due to the matrix isolation experiments (Section VIII,B), Chapman reinterpreted all the above photolysis experiments, replacing the bicyclic azirine (**162**) by the ketenimine (**183**).⁴⁹ The new general mechanism, replacing



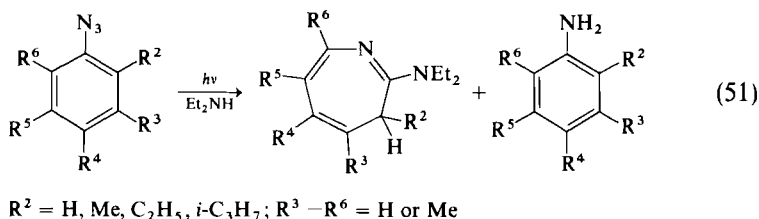
SCHEME 38

Scheme 37, is shown in Scheme 38. The application of the same mechanism to the thermal reactions follows.

There can now be little doubt that **183** is the longest lived C_6H_5N intermediate, and that it is the species trapped by nucleophiles. Yet, either **162** or **161** may still play a role, for instance in annelated systems where the relative energies can be reversed. If the postulate of DeGraff *et al.*²⁴⁰ of two species in equilibrium is correct, then Eq. (49) can be reinterpreted as shown in Eq. (50), with **183** as the more stable species.

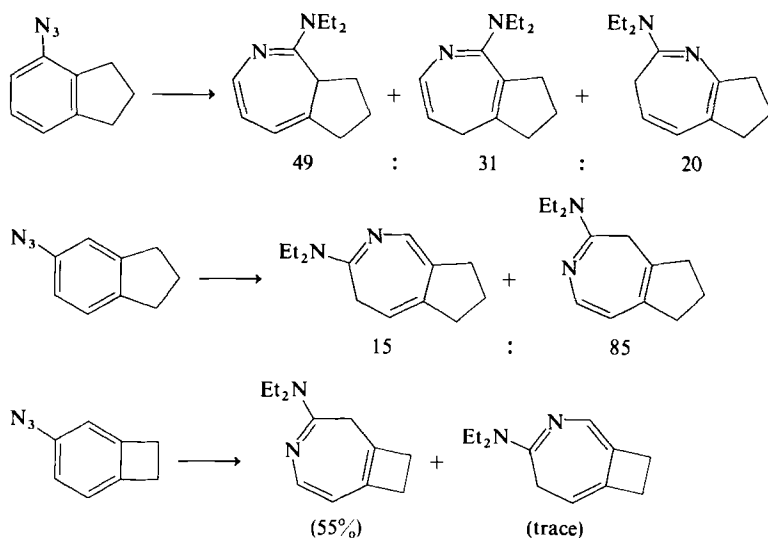


Although the thermal azepine formation from aryl azides is of rather limited synthetic potential,^{7,174} the photochemical reaction has some generality. Sundberg *et al.* obtained 3*H*-azepines in yields of 33–67% along with the corresponding anilines and other by-products by photolysis of a variety of substituted phenyl azides in diethylamine (Eq. 51). When only one ortho substituent was present, the ring expansion usually occurred in the direction away from this substituent. The transient 1*H*-azepines were detected.²³⁶

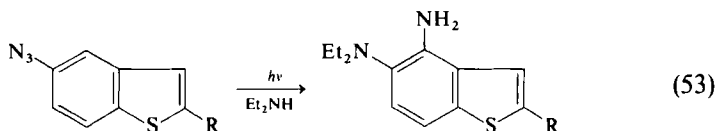
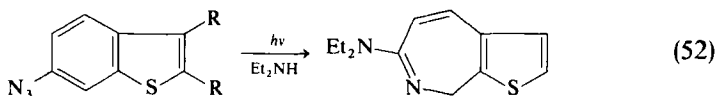


Carde and Jones²⁴¹ obtained annelated azepines by photolysis of hydrogenated cyclobutaphenyl and cyclopentaphenyl azides in diethylamine (Scheme 39). Here too, migration of the nitrene away from the substituent (i.e., the ring junction) predominated. No azepine was obtained from 2-azidobiphenylene.

²⁴¹ R. N. Carde and G. Jones, *J. C. S. Perkin I*, 519 (1975).



The first attempts to apply the ring expansion to the azides of naphthalene and other condensed aromatics were unencouraging.^{242–244} Only 6-azido-benzo[*b*]thiophenes afforded the corresponding thienozepines in fair yields (Eq. 52).²⁴⁵ The analogous 5-azido-benzo[*b*]thiophenes gave no azepines, but only diaminobenzothiophenes (Eq. 53).²⁴⁴ *o*-Diamines were also obtained



in good yields from 2-azidonaphthalene and 7-azidoquinoline in a variety of secondary amines (Eq. 54).²⁴⁶

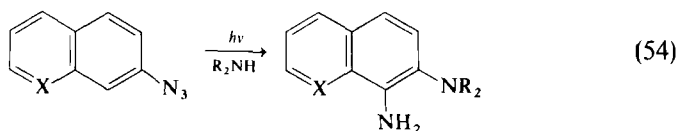
²⁴² R. Huisgen and M. Appl, *Chem. Ber.* **91**, 12 (1958).

²⁴³ S. E. Hilton, E. F. V. Scriven, and H. Suschitzky *Chem. Commun.*, 853 (1974).

²⁴⁴ B. Iddon, H. Suschitzky, and D. S. Taylor, *J. C. S. Perkin I*, 579 (1974).

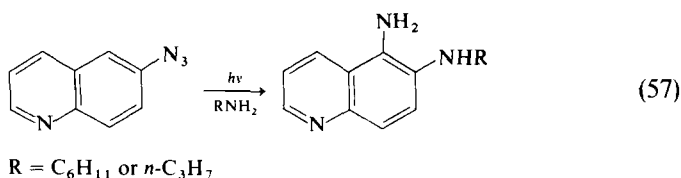
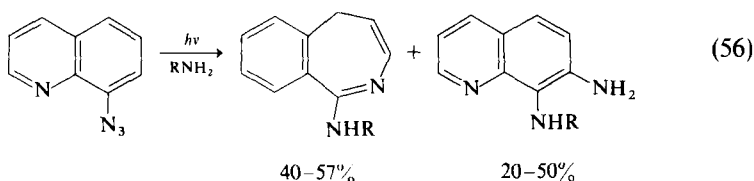
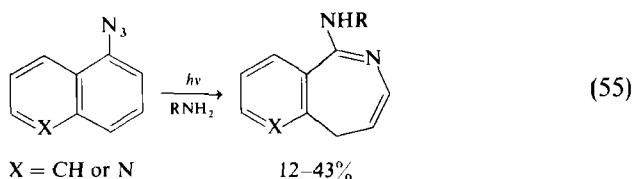
²⁴⁵ B. Iddon, M. W. Pickering, and H. Suschitzky, *Chem. Commun.*, 759 (1974).

²⁴⁶ S. E. Carroll, B. Nay, E. F. V. Scriven, and H. Suschitzky, *Synthesis*, 710 (1975).

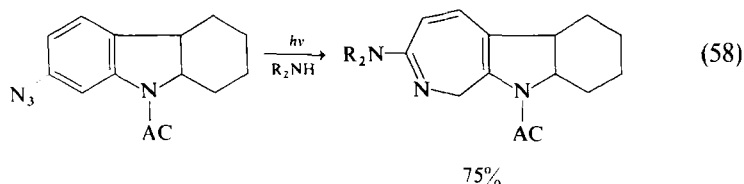


X = CH or N

Further studies showed that annelated azepines could be obtained from the photolysis of 1-naphthyl azide and 5- and 8-azidoquinolines in the presence of primary amines.²⁴⁷ However, 6- and 7-azidoquinoline again gave only the *o*-diamines (Eqs. 55–57).²⁴⁷



Ring expansion of a hexahydrocarbazole was also observed (Eq 58).²⁴⁸

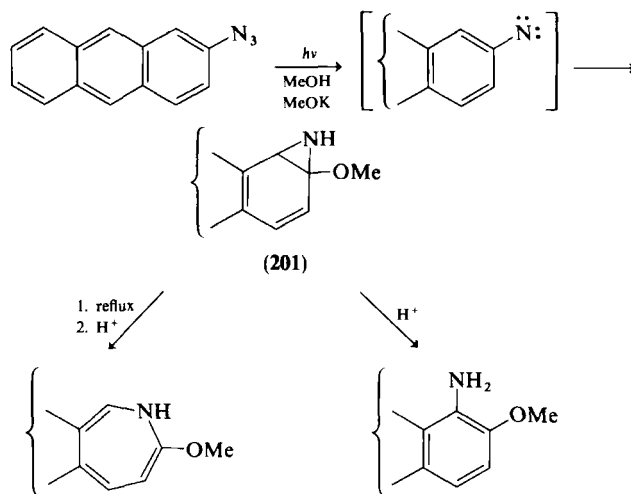


Rigaudy *et al.* reported that nearly quantitative yields of azepines can be obtained from such photolyses merely by improving the nucleophilicity of

²⁴⁷ B. Nay, E. F. V. Scriven, H. Suschitzky, and Z. U. Khan, *Synthesis*, 757 (1977).

²⁴⁸ E. F. V. Scriven, H. Suschitzky, D. R. Thomas, and R. F. Newton, *J. C. S. Perkin I*, 53 (1979).

the medium using concentrated KOMe in methanol.²⁴⁹ Furthermore, it was convincingly shown that the irradiated solution contained an intermediate, which after refluxing and neutralization gave the azepine, whereas acid treatment immediately after the photolysis gave the corresponding *o*-diamine. This behavior, together with the UV spectrum of the solution containing the intermediate formed by irradiation of 2-azidoanthracene strongly indicated that the intermediate was the dihydroanthraceno[1,2-*b*]azirine **201** (Scheme 40).²⁴⁹ Analogous results were obtained with 2-naphthyl azide²⁴⁹ and with 1-phenyl- and 1-methoxy-2-azidoanthracenes.²⁵⁰

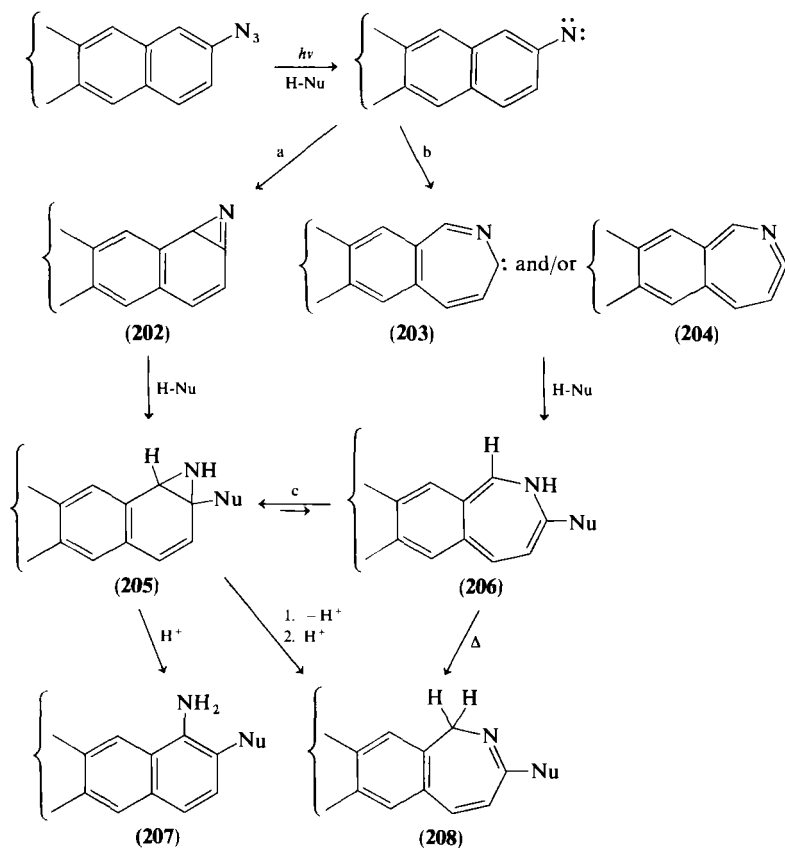


SCHEME 40

The question is now: how is the aziridine **201** formed^{249,250}? Until recently, it has been assumed^{12,243–249} that *o*-diamine formation is indicative of trapping of a bicyclic *azirine* (**202**, Scheme 41, path a). The new possibility, due to Chapman's matrix isolation experiments (Section VIII,B) and our previous suggestion,²¹⁷ is quite different (Scheme 41, path b). According to path b, an azacycloheptatrienylidene²¹⁷ (**203**) or an azacycloheptatetraene⁴⁹ (**204**) is trapped by the nucleophile, giving an *o*-quinoid 1*H*-azepine (**206**) in the naphthalene, anthracene, quinoline, and benzo[*thiophene*] series. Valence tautomerization to the aziridine **205** (Scheme 41, path c) will be particularly favorable in these cases. Compound **205** is the observable intermediate.^{249,250} When 1*H*-azepines like **206** are *not* destab-

²⁴⁹ J. Rigaudy, C. Igier, and J. Barcelo, *Tetrahedron Lett.*, 3845 (1975).

²⁵⁰ J. Rigaudy, C. Igier, and J. Barcelo, *Tetrahedron Lett.*, 1837 (1979).



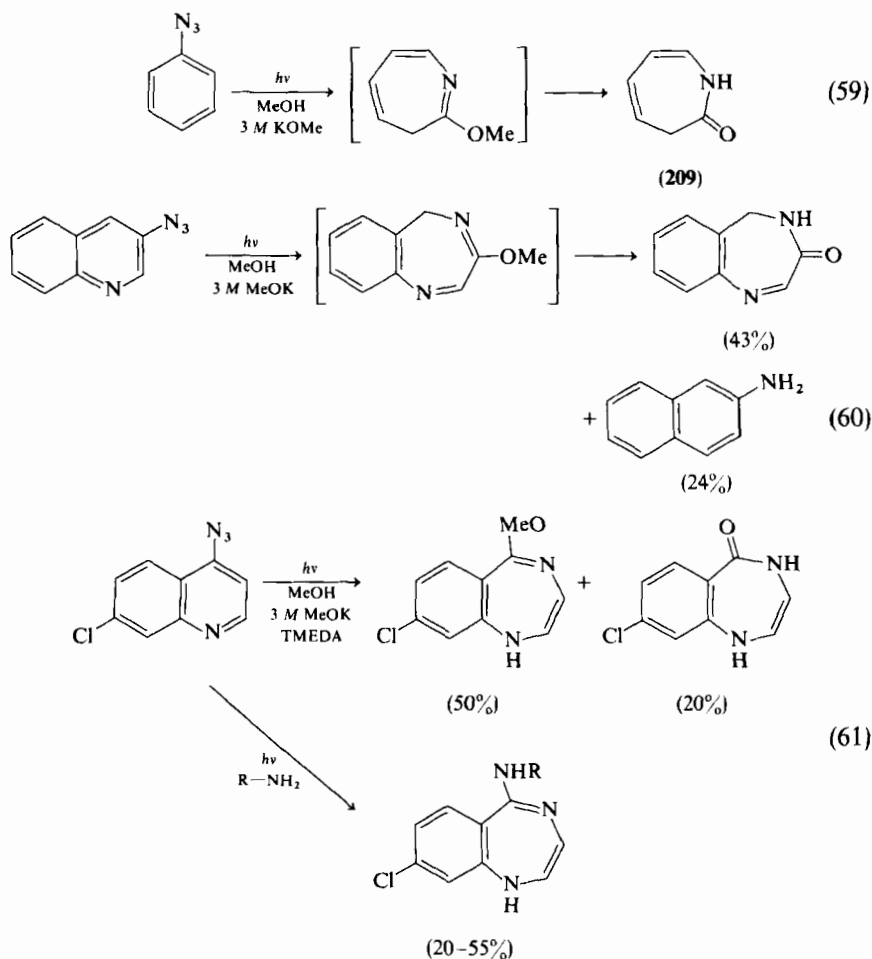
SCHEME 41

ilized by annelation, they are directly observable.²³⁶ Immediate acid treatment of **205** now gives the *o*-diamine **207**. Heating the strongly basic solution under reflux allows tautomerization back to **206** and then to **208**, or by reversible deprotonation a direct transformation of **205** to **208**.

The use of a strongly basic solvent has also permitted trapping of the intermediate from phenyl azide with methanol.²⁵¹ The product **209** was isolated in up to 48% yield when the reaction was carried out in the presence of 18-crown-6 (Eq. 59). Diazepines were obtained in a similar manner from 3- and 4-azidoquinolines (Eqs. 60–61).²⁵²

²⁵¹ E. F. V. Scriven and D. R. Thomas, *Chem. Ind. (London)*, 385 (1978).

²⁵² F. Hollywood, E. F. V. Scriven, H. Suschitzky, and D. R. Thomas, *Chem. Commun.*, 806 (1978).



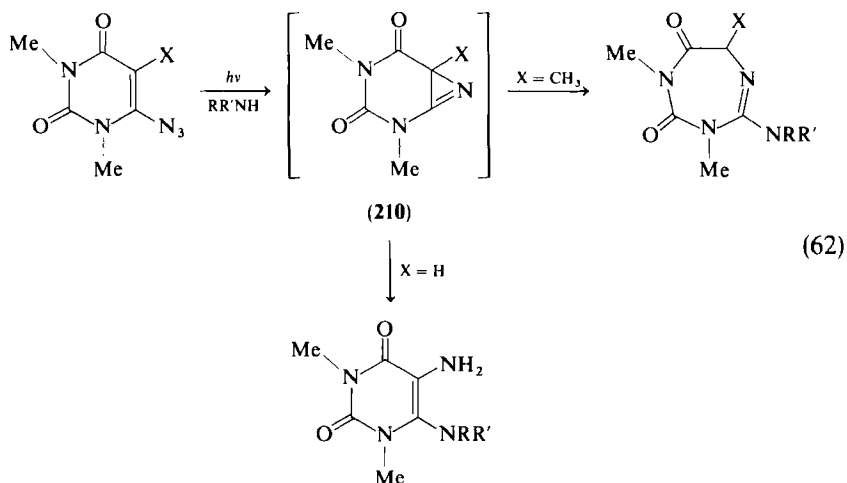
Attempts to use H_2S as a trapping agent met with very limited success; the thione related to **209** was formed in low yield.²³⁵ *o*-Mercaptoamines have generally been obtained on photolysis in the presence of mercaptans.^{248,253}

Diaminopyrimidinediones and/or triazepinediones have been prepared by photolysis of 6-azidopyrimidine-2,4-diones (Eq. 62).^{254,255} Trapping with methanol occurred similarly.²⁵⁵ The reactive intermediate was assumed to be the azirine **210**, and this may be justified in these systems in view of the fact that vinyl azides do give stable azirines [see Eqs. (4) and (5); Section II,A].

²⁵³ S. E. Carroll, B. Nay, E. F. V. Scriven, H. Suschitzky, and D. R. Thomas, *Tetrahedron Lett.*, 3175 (1977).

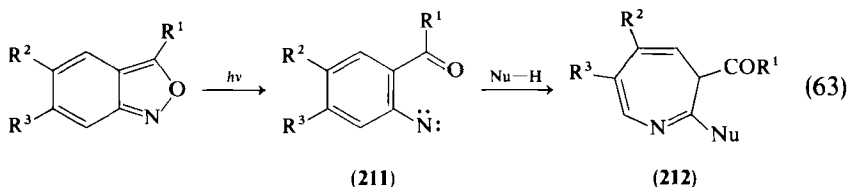
²⁵⁴ S. Senda, K. Hirota, T. Asao, and K. Maruhashi, *J. Am. Chem. Soc.* **100**, 7661 (1978).

²⁵⁵ S. Senda, K. Hirota, T. Asao, K. Maruhashi, and N. Kitamura, *Tetrahedron Lett.*, 1531 (1978).



2. From Anthranils, Indazoles, and Related Azides

The photolysis of anthranils in methanol or amines gives 2-methoxy- or 2-amino-3*H*-azepines (**212**), suggestive of initial opening of the anthranil to a nitrene (**211**) (Eq. 63).²⁵⁶



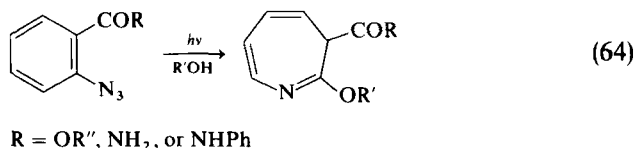
$R^1 = \text{Ph or Me}; R^2, R^3 = \text{H or Cl}; \text{NuH} = \text{MeOH, Et}_2\text{NH, or PhNH}_2$

In agreement with this, Berwick²⁵⁷ obtained azepines from the photolyses of *o*-azidoacetophenone as well as from 3-methylanthranil in piperidine. Notably, the azepines obtained from anthranils correspond to a migration of the nitrene away from the acyl substituent (see **212**).^{256,257} In contrast, *o*-azidoacetophenone gave about a 1:1 ratio of the two azepines resulting from migration toward or away from the substituent.²⁵⁷ Good yields of azepines were obtained by photolysis of several *o*-acylphenyl azides in alcohol (Eq. 64).²⁵⁸

²⁵⁶ M. Ogata, H. Matsumoto, and H. Kano, *Tetrahedron* **25**, 5205 (1969).

²⁵⁷ M. A. Berwick, *J. Am. Chem. Soc.* **93**, 5780 (1971).

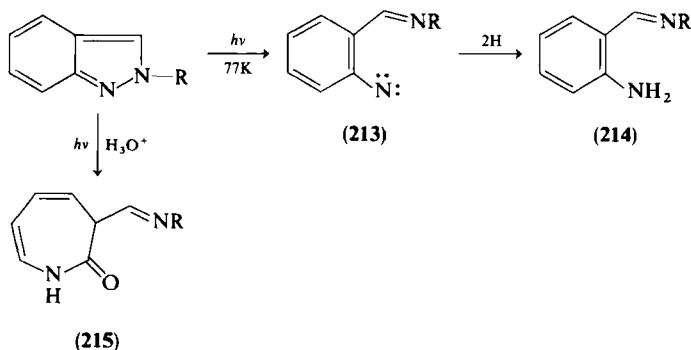
²⁵⁸ R. Purvis, R. K. Smalley, W. A. Strachan, and H. Suschitzky, *J. C. S. Perkin I*, 191 (1978); A. C. Mair and M. F. G. Stevens, *J. Chem. Soc. C*, 2317 (1971).



However, the azepine yield was low when a 5-OMe substituent was present, and no azepine was formed from the 5-NO₂ compound. This is possibly due to a rapid singlet-triplet crossing in the nitro compound; the triplet nitrene then gives the corresponding azo compound.²⁵⁸ With the acyl group in meta or para position with respect to the nitrene, the azepine yields were lower. It was concluded that a reasonably electrophilic singlet nitrene is essential for azepine formation.²⁵⁸

The formation of anthranils by thermolysis of *o*-acylphenyl azides is not a nitrene reaction.²⁵⁹

The photolysis of 2-alkylindazoles at 77 K in glassy solvents gives an unstable intermediate with an absorption at about 600 nm in the UV, which was tentatively assigned to the triplet nitrene **213**.²⁶⁰ The imines **214**, formed from the nitrene by hydrogen abstraction from the solvent, were isolable. Photolysis in the presence of acids gave azepinones (**215**).²⁶¹



3. From Hydroxylamine Derivatives

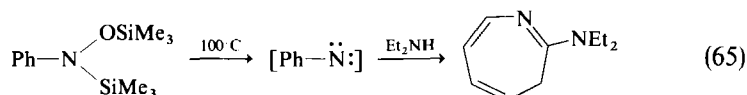
The formation of phenylnitrene by thermolysis of *O,N*-bis(trimethylsilyl)-*N*-phenylhydroxylamine at 100°C has an activation enthalpy of 27.7 kcal/mol and is supported by the formation of aniline, azobenzene, or an 85–95% yield of 2-diethylamino-3*H*-azepine in the presence of diethylamine (Eq. 65).²⁶²

²⁵⁹ J. H. Hall, F. E. Behr, and R. L. Reed, *J. Am. Chem. Soc.* **94**, 4952 (1972).

²⁶⁰ W. Heinzelmann, *Helv. Chim. Acta* **61**, 618 (1978).

²⁶¹ W. Heinzelmann, M. Märky, and P. Gilgen, *Helv. Chim. Acta* **59**, 2362 (1976).

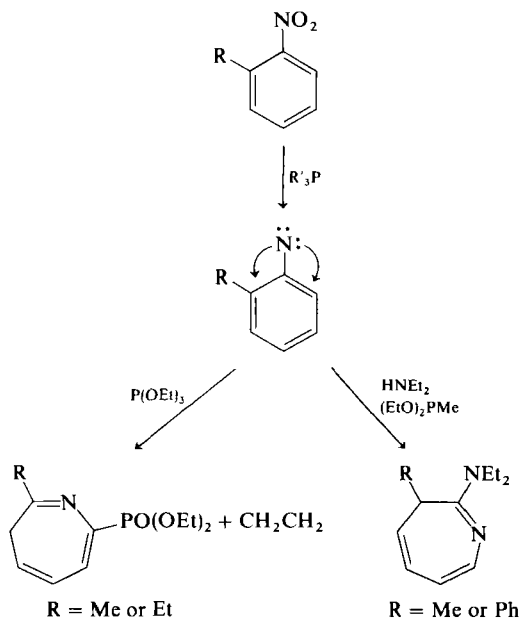
²⁶² F. P. Tsui, Y. H. Chang, T. M. Vogel, and G. Zon, *J. Org. Chem.* **41**, 3381 (1976).



This is the highest reported yield of an azepine from phenylnitrene.

4. From Nitro and Nitroso Compounds

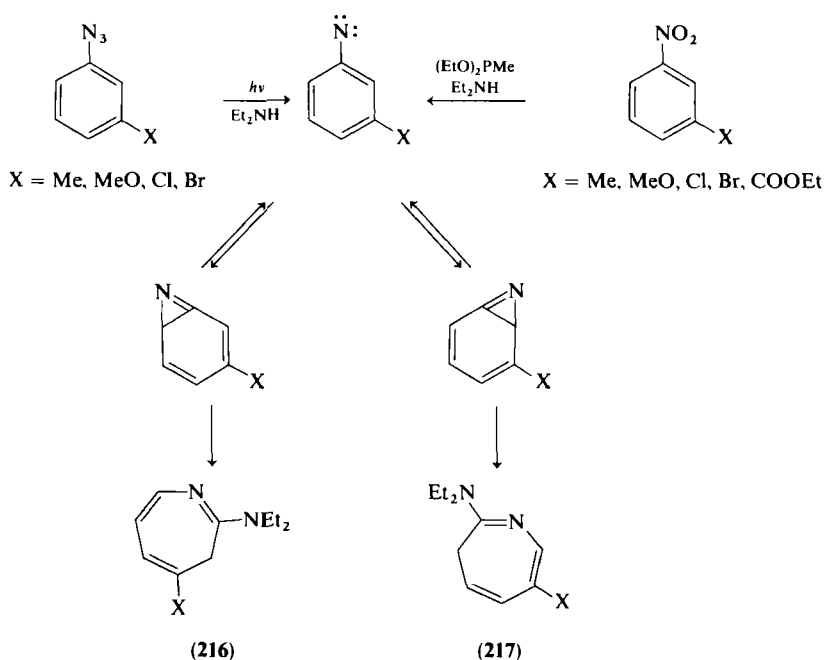
Much of the work on deoxygenation of aromatic nitro and nitroso compounds by tervalent phosphorus reagents has been reviewed.³ Triethyl phosphite has been used frequently, but diethyl methylphosphonite was found to be superior for the deoxygenation of nitro compounds.^{3,263} The isolation of azepines from such reactions (Scheme 42) indicated the initial formation of arylnitrenes. However, a marked influence of the nucleophile upon the direction of the apparent migration of the nitrene—away or toward an ortho substituent—was noted (Scheme 42).²⁶⁴ Evidence that the *same* intermediates are involved in the azepine forming reactions from phenyl azides and nitrobenzenes was obtained by a careful examination of the azepines formed from meta-substituted derivatives (Scheme 43). The ratios of the azepines **216** and



SCHEME 42

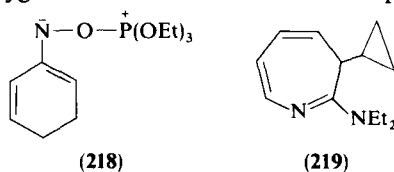
²⁶³ J. I. G. Cadogan and M. J. Todd, *J. Chem. Soc. C*, 2808 (1969).

²⁶⁴ J. I. G. Cadogan, D. J. Sears, D. M. Smith, and M. J. Todd, *J. Chem. Soc. C*, 2813 (1969).



SCHEME 43

217 were virtually identical in the two sets of reactions.²⁶⁵ It is without importance for this argument whether the trappable intermediates are the bicyclic azirines,²⁶⁵ as shown in Scheme 43, or the related azacycloheptatetraenes. It was recognized that phosphorylated species such as **218** rather than free nitrenes could be the immediate precursor of the trappable intermediates in the deoxygenation reactions.²⁶⁵ Several reports have shown that



compounds related to **218** can be formed in deoxygenations and behave in a way different from free nitrenes.²⁶⁶⁻²⁶⁸

²⁶⁵ T. de Boer, J. I. G. Cadogan, H. M. McWilliam, and A. G. Rowley, *J. C. S. Perkin II*, 554 (1975).

²⁶⁶ P. K. Brooke, R. B. Herbert, and E. G. Holliman, *Tetrahedron Lett.*, 761 (1973).

²⁶⁷ R. J. Sundberg and R. H. Smith, *J. Org. Chem.* **36**, 295 (1971); R. J. Sundberg and C. C. Lang, *ibid.*, 300.

²⁶⁸ R. A. Abramovitch and S. R. Challand, *Chem. Commun.*, 1160 (1972); R. A. Abramovitch, J. Court, and E. P. Kyba, *Tetrahedron Lett.*, 4059 (1972).

For the reactions shown in Scheme 43 it was found that electron-withdrawing substituents (X) favored migration of the nitrene *toward* this substituent, giving **217**. *m*-Methyl had no directing effect, and the opposite (favoring **216**) was found for an electron-releasing substituent (*m*-OCH₃).²⁶⁵ Similar effects were noted in a related study using meta-substituted nitrobenzenes (X = Ph, 4-pyridyl, Me, Cl, OMe, Et₂NCO, CH₃CO).²⁶⁹

The reaction of 2-cyclopropylnitrosobenzene with P(OEt)₃ and triethylamine to give the azepine **219** (38%), where the nitrene has migrated away from the substituent, has been reported.²⁷⁰

5. Directing Effects in Arylnitrene Ring Expansion

The directing effects mentioned above [Eq. (51),²³⁶ Scheme 39,²⁴¹ Eqs. (63–64),^{256–258} Scheme 42,^{264,270} and Scheme 43^{265,269}] are probably the result of several contributing factors, but some apparent generalities may be noted. First of all, the influence of the nucleophile (see Scheme 42) has been ascribed to steric hindrance of attack of the larger nucleophile [EtO)₃P] on the trappable intermediate (assumed to be the equilibrating bicyclic azirines) from ortho-substituted nitrenes.²⁶⁵ In the absence of this effect, migration of the nitrene *away* from the substituent may be expected on dynamic grounds.²¹⁸

In addition to these effects, electronic effects on the azacycloheptatetraene intermediates may hold the key to an understanding of the selectivities. Scheme 44 shows all the possible intermediates, which for simplicity are supposed to be in equilibrium. Ortho substituents (R = alkyl or aryl) would be expected to stabilize the ketenimines **222** more than **225**, thus leading to the observed dominant regiochemistry. On the other hand, when R = *o*-acyl, **222** would be destabilized electronically, presumably more so than **225**. Electronegatively substituted ketenimines appear to be generally unstable.^{29,271,272} If thermodynamic equilibrium prevails, **225** would then dominate, but **222** would be more reactive toward nucleophiles. The products derived from both were obtained.²⁵⁷

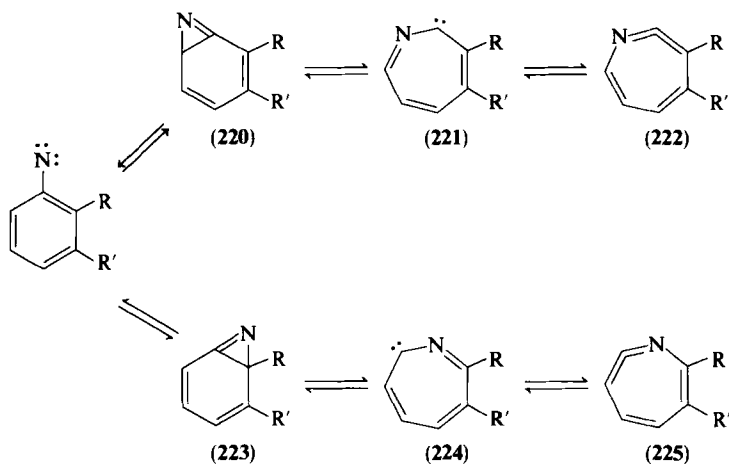
The directing effect of meta substituents (R' in Scheme 44) can be rationalized in a similar manner: the closer an electronegative substituent is to the carbenic center in **221** or **224** (or the corresponding atom in **222** and **225**),

²⁶⁹ F. R. Atherton and R. W. Lambert, *J. C. S. Perkin I*, 1079 (1973).

²⁷⁰ S. S. Mochalov, A. N. Fedotov, A. I. Sizov, and Yu. S. Shabarov, *Zh. Org. Khim.* **15**, 1425 (1979).

²⁷¹ R. B. Woodward and D. J. Woodman, *J. Am. Chem. Soc.* **88**, 3169 (1966).

²⁷² C. Wentrup and W. Reichen, *Helv. Chim. Acta* **59**, 2615 (1976); H.-M. Berstermann, R. Harder, H.-W. Winter, and C. Wentrup, *Angew. Chem., Int. Ed. Engl.* **19**, 564 (1980).



SCHEME 44

the more it will destabilize the system. Electron-donating groups have the opposite effect.

The directions of ring expansion in condensed aromatic nitrenes are relatively easy to explain. The nitrene always moves toward the carbon atom with the highest electron density [e.g., 2-naphthyl nitrene inserts into the 1,2-bond, not the 2,3-bond; see Eqs. (52–61) and Scheme 41]. This is to be expected for the addition of an electrophilic singlet nitrene to a double bond, and it indicates that an azirine is either an intermediate or a transition state in the ring expansion (see also Section VIII,H,2).

It should be noted that there are several examples of expansion of condensed nitrenes and carbenes in the “wrong” direction. This was discussed in Section VIII,A (see Schemes 33–35).

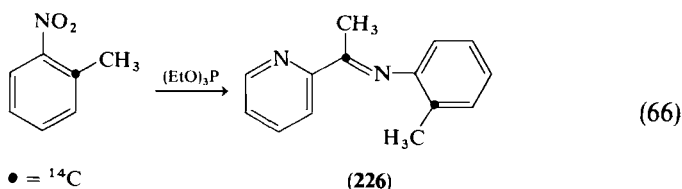
D. FORMATION OF PYRIDINES

Sunberg found that the triethyl phosphite deoxygenation of ortho-substituted nitroaromatics resulted in variable amounts of *N*-aryl-2-acetimidylpyridines²⁷³ along with azepines²⁷⁴ as described above and other products. A subsequent labeling study settled the mechanistic speculation and established the overall rearrangement as shown in Eq. (66).²⁷⁵ This, taken with

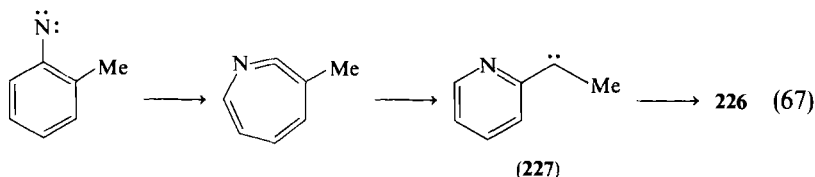
²⁷³ R. J. Sundberg, *J. Am. Chem. Soc.* **88**, 3781 (1966).

²⁷⁴ R. J. Sundberg, B. P. Das, and R. H. Smith, *J. Am. Chem. Soc.* **91**, 658 (1969).

²⁷⁵ R. J. Sundberg and S. R. Suter, *J. Org. Chem.* **35**, 827 (1970).



the results from other substituted nitrobenzenes,^{274,276} is in accord with a mechanism *formally* involving a nitrene-carbene rearrangement which can now be formulated as in Eq. (67). A similar mechanism had already been



advanced²⁷⁶ and later abandoned²⁷⁴ by Sundberg *et al.* A modified mechanism has been proposed by Cadogan.³ A further example of the formation of a compound related to **226** by deoxygenation of 2,5-di(*tert*-butyl)nitrosobenzene has been reported.²⁷⁷ The only disadvantage of the mechanism shown in Eq. (67) is that the carbene **227**, being an alkylcarbene, would be expected to undergo an extremely rapid 1,2-hydrogen shift,²⁷⁸ giving 2-vinylpyridine. No such compound was isolated. This suggests that the species shown in Eq. (67) are not free, but complexed with triethyl phosphite.^{200,274} In agreement with this, no trace of compound **226** was produced from the photolysis of azidotoluenes.²⁷⁴ Proof that a nitrene-carbene rearrangement of the type designated in Eq. (67) would indeed give rise to a vinylpyridine was obtained by flash vacuum pyrolysis of the carbene precursor **228** (R = H) which gave a quantitative yield of 2-vinylpyridine (**229**).¹⁹⁹ The azide **231** gave an 8% yield of **229**, the main product (30%) being the amine **230**.²⁰⁰ These results indicate that the nitrene-carbene equilibrium is in favor of the nitrene in the gas phase¹⁰ (see also Section VIII,A).

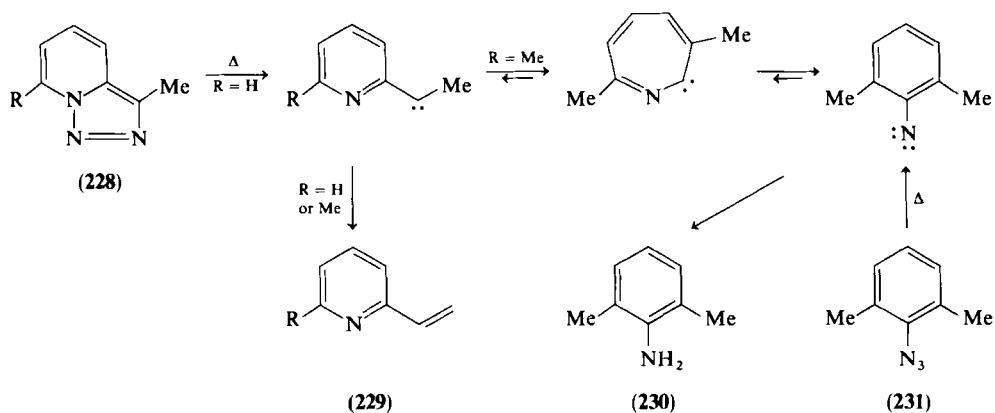
Moore and co-workers²⁷⁹ have reported an extraordinary example of formation of a pyridine ring by thermal decomposition of an azide in solution. The reaction (Eq. 68) was interpreted on the basis of the mechanism given in Scheme 45.

²⁷⁶ R. J. Sundberg, W. G. Adam, R. H. Smith, and D. E. Blackburn, *Tetrahedron Lett.*, 777 (1968).

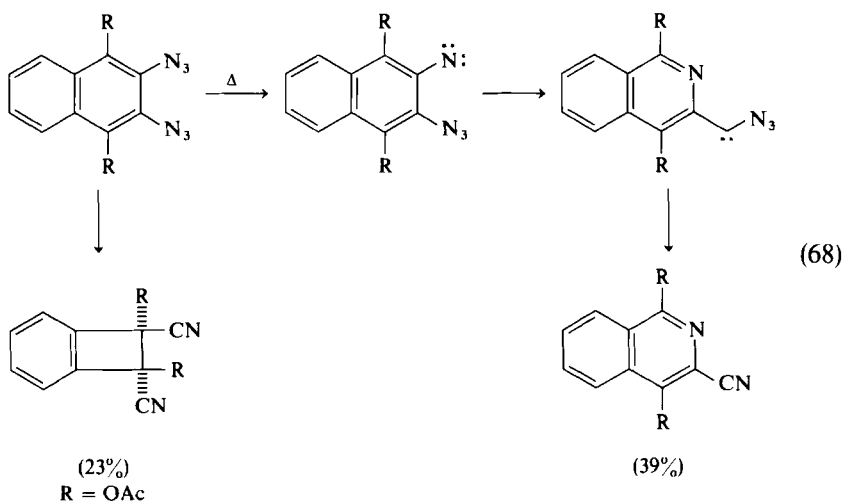
²⁷⁷ L. R. C. Barclay, P. G. Khazanie, K. A. H. Adams, and E. Reid, *Can. J. Chem.* **55**, 3273 (1977).

²⁷⁸ H. F. Schaefer, *Acc. Chem. Res.* **12**, 288 (1979).

²⁷⁹ D. S. Pearce, M.-S. Lee, and H. W. Moore, *J. Org. Chem.* **39**, 1362 (1974).



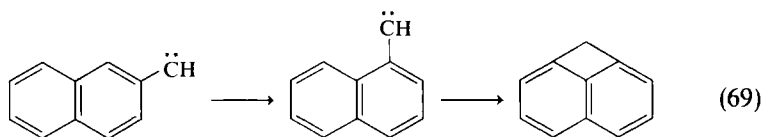
SCHEME 45



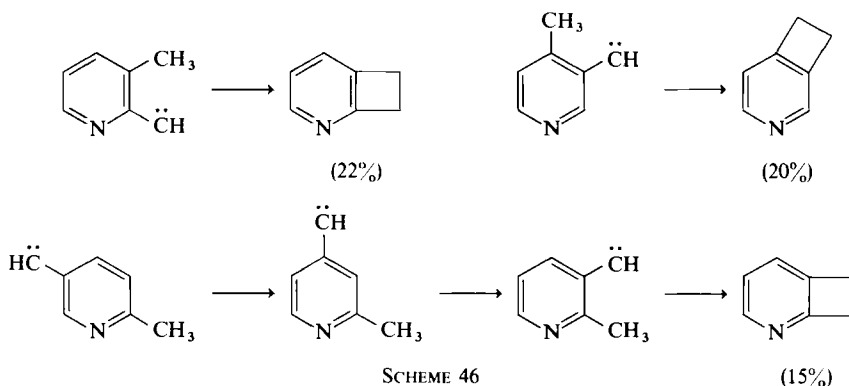
E. INSERTION INTO AN ORTHO SIDE CHAIN TO GIVE A FOUR-MEMBERED RING

Cyclizations of carbenes and nitrenes to form four-membered rings are extremely rare, but when no other options are available for the reactive species, such processes will occur. Thus, cyclobuta[de]naphthalene is formed in better than 40% yield from 1-naphthylcarbene in the gas phase. The same

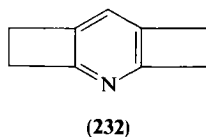
product is also obtained from 2-naphthylcarbene via a carbene-carbene rearrangement (Eq. 69).²⁸⁰



o-Tolylcarbene inserts into the methyl group, giving benzocyclobutene.¹⁰ Similarly, cyclobutapyridines are obtained from methylpyridylcarbenes.²⁰⁴ When the two groups are not originally ortho related, the reaction proceeds by carbene-carbene rearrangement (Scheme 46).²⁰⁴



It is not clear whether the formation of cyclobutaarenes by flash pyrolysis of *o*-(chloromethyl)methylarenes involves arylcarbenes,* but the formation of phenylcarbene from benzyl fluoride²⁰⁷ is at least suggestive. 1,2,4,5-Tetrahydrodicyclobuta[*b,e*]pyridine (**232**) has been prepared in 30% yield by such a method.²⁸¹



* In fact, it does not.^{280a}

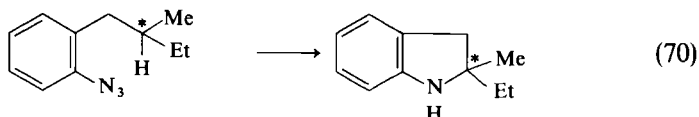
²⁸⁰ J. Becker and C. Wentrup, *Chem. Commun.*, 190 (1980).

^{280a} M. J. Morello and W. S. Trahanovsky, *Tetrahedron Lett.*, 4435 (1979).

²⁸¹ A. Naiman and K. P. C. Vollhardt, *Angew. Chem.* **91**, 440 (1979); *Angew. Chem., Int. Ed. Engl.* **18**, 411 (1979).

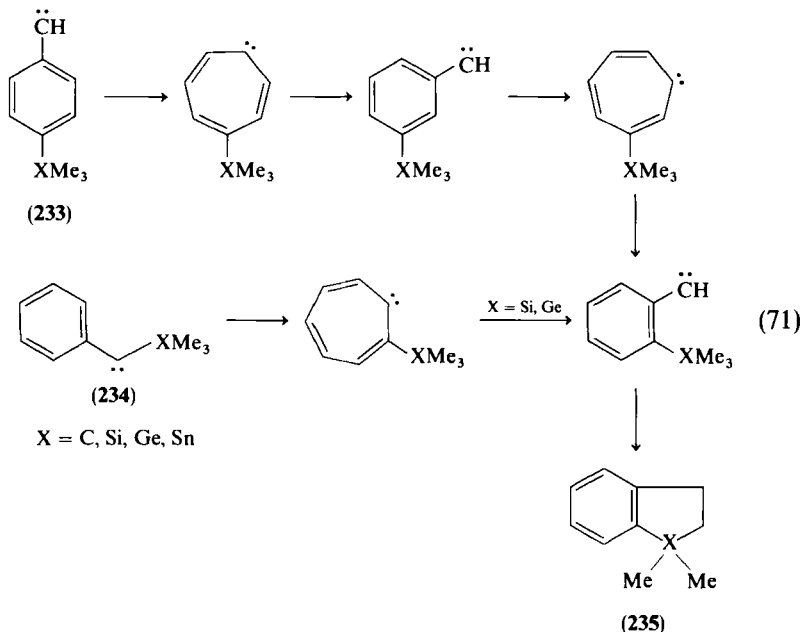
F. INSERTION INTO A SATURATED SIDE CHAIN TO GIVE A FIVE-MEMBERED RING

Singlet phenylnitrene inserts with 100% retention of configuration into an optically active side chain when the reaction is carried out in the gas phase; in solution, only 60% retention was observed, due to partial deactivation to the triplet ground state. Thus, the singlet inserts in one step, the triplet via abstraction (Eq. 70).⁷ Evidence has been presented for a triplet nitrene in



the analogous insertion of 2,4,6-tri-*tert*-butylphenylnitrene as generated by deoxygenation of the corresponding nitroso compound.²⁷⁷

Good to excellent yields of 1-sila-, 1-germa-, and 1-stannaindanes (**235**) have been obtained by multiple carbene-carbene rearrangements (Eq. 71). The initial carbenes **233** and **234** were formed by flash pyrolysis of the corresponding phenyldiazomethanes at 400–600°C.^{282–284}

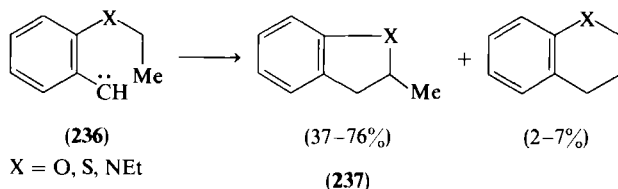


²⁸² A. Sekiguchi and W. Ando, *Bull. Chem. Soc. Jpn.* **50**, 3067 (1977).

²⁸³ G. R. Chambers and M. Jones, *Tetrahedron Lett.*, 5193 (1978).

²⁸⁴ W. Ando, A. Sekiguchi, A. J. Rothschild, R. R. Gallucci, M. Jones, T. J. Barton, and J. A. Kilgour *J. Am. Chem. Soc.* **99**, 6995 (1977).

Insertion of arylcarbenes (**236**) into ortho side chains giving dihydro-benzofurans and related compounds (**237**) has also been described.^{282,285} The formation of five-membered rings (**237**) predominates in such reactions.²⁸⁵ The required carbenes **236** can be generated either directly from



the ortho-substituted aryldiazomethanes,²⁸⁵ or via carbene-carbene rearrangement from the para-substituted aryldiazomethanes.²⁸²

G. INSERTION INTO AN UNSATURATED SIDE CHAIN TO GIVE A FIVE-MEMBERED RING

To this group of reactions belong the nonnitrene cyclizations of aryl azides with *o*-nitro-, acyl-, and thioacyl groups, giving benzofuroxans,⁵⁷ anthranils,^{258,286-289} and thioanthranils,²⁹⁰ respectively. Nitrenes are probably not involved either in the cyclizations onto imidyl-^{291,292} and azo groups,^{7,293} which give 2*H*-indazoles and 2*H*-benzotriazoles, respectively. In the latter case, the kinetics indicates initial 1,3-dipolar addition of the azide onto the azo group.²⁹³

The formation of indoles by deoxygenation of *o*-nitrostyrenes was found to be consistent with an intermediate of the type **238**.²⁹⁴ The aptitude of migration of a phenyl group toward the positively charged 3-position was at least 25 times larger than for a methyl group.²⁹⁴ The nature of Y in the

²⁸⁵ W. D. Crow and H. McNab, *Aust. J. Chem.* **32**, 99, 111, 123 (1979).

²⁸⁶ W. Friedrichsen and P. Kaschner, *Justus Liebigs Ann. Chem.*, 1959 (1977).

²⁸⁷ W. Ried and J. B. Mavunkal, *Chem. Ber.* **111**, 1521, (1978).

²⁸⁸ R. K. Smalley, R. H. Smith, and H. Suschitzky *Tetrahedron Lett.*, 2309 (1978); 4687 (1979).

²⁸⁹ L. M. Gornostaev, V. A. Levanskii, and E. P. Fokin, *Zh. Org. Khim.* **15**, 1692 (1979).

²⁹⁰ J. Ashby and H. Suschitzky, *Tetrahedron Lett.*, 1315 (1971).

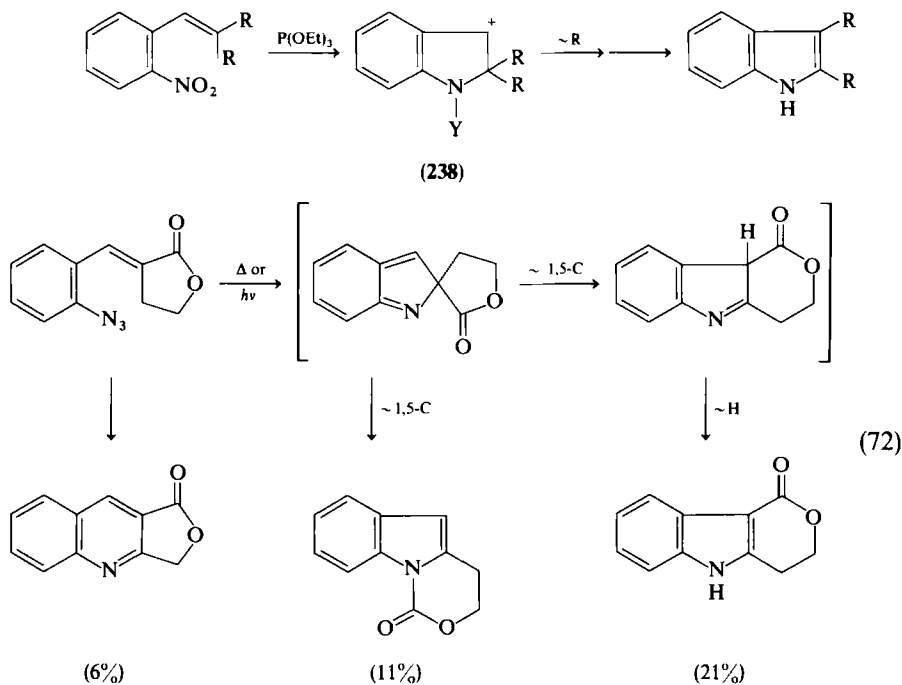
²⁹¹ L. Krbecek and H. Takimoto, *J. Org. Chem.* **29**, 1150 (1964).

²⁹² T. J. Schwan, LeRoy J. Honkomp, C. S. Davis, and G. S. Lougheed, *J. Pharm. Sci.* **67**, 1022 (1978).

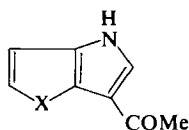
²⁹³ J. H. Hall and F. W. Dolan, *J. Org. Chem.* **43**, 4608 (1978).

²⁹⁴ R. J. Sundberg, "The Chemistry of Indoles," Chapter III E, p. 183-188. Academic Press, New York, 1970; R. J. Sundberg and G. S. Kotchmar, *J. Org. Chem.* **34**, 2285 (1969); R. J. Sundberg, L.-S. Lin, and D. E. Blackburn, *J. Heterocycl. Chem.* **6**, 441 (1969); R. J. Sundberg, H. F. Russell, W. V. Ligon, and L.-S. Lin, *J. Org. Chem.* **37**, 719 (1972).

intermediate **238** was not specified, but it could well be a phosphorylated nitro or nitroso group as indicated by the isolation of *N*-hydroxyindoles in some cases.²⁹⁴ If free nitrenes were formed in such reactions, the intermediate **238** would in fact be a 2*H*-indole, and migration of a group *R* toward both nitrogen and carbon could be expected. Evidence for just such a process has been presented by Zimmer and Downs,²⁹⁵ who used an azide as precursor (Eq. 72). A free nitrene could well be involved in this reaction.



3-Azido-2-vinyl-furans, -thiophenes, -selenophenes,²⁹⁶ and -*p*-benzoquinones³⁷ cyclize to the corresponding annelated pyrroles (e.g., **239**).

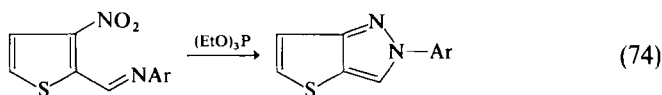
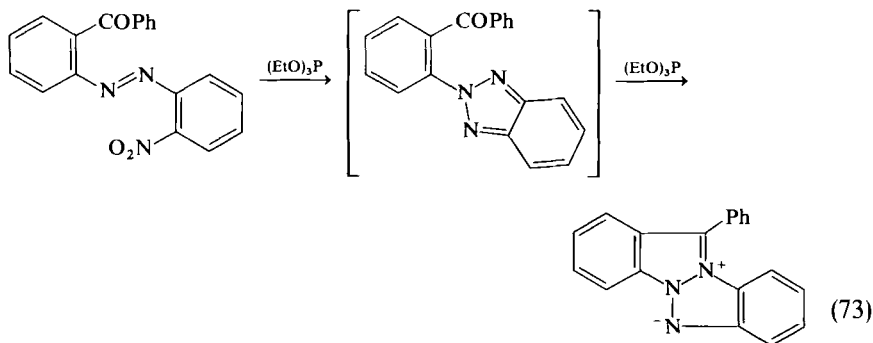


(239)

²⁹⁵ H. Zimmer and B. Downs, *J. Heterocycl. Chem.* **15**, 703 (1978).

²⁹⁶ S. Gronowitz, C. Westerlund, and A.-B. Hörnfeldt, *Acta Chem. Scand., Ser. B* **30**, 391 (1976).

The same types of products as described above are also obtained by triethyl phosphite deoxygenation of the corresponding nitroaromatics.^{3,292,297-299} Examples are shown in Eqs. (73)²⁹⁸ and (74).²⁹⁹ Free



nitrenes or, more likely, phosphorylated "nitrenoids" may be involved in such reactions³ (cf. Section VIII,C,4). Kametani⁹ has summarized the deoxygenative cyclizations of β -ethoxycarbonyl-*o*-nitrostyrenes, which lead to pyridine derivatives.

Formally related is also the photocyclization of 8-azido-1-arylazonaphthalenes to benzo[*cd*]indazole-*N*-arylimines.³⁰⁰

H. CYCLIZATION ONTO AN ADJACENT RING

1. By Direct Cyclization

Carbazoles are formed—often in high yields—by thermolysis or photolysis of 2-azidobiphenyls,^{7,174} by photolysis of 2-isocyanatobiphenyls,³⁰¹ and by deoxygenation of the related 2-nitroaromatics^{3,302} (Eq. 75). The early work on these reactions has been extensively reviewed,^{1-3,7,174} and

²⁹⁷ M.-A. Armour, J. I. G. Cadogan, and D. S. B. Grace, *J. C. S. Perkin II*, 1185 (1975).

²⁹⁸ J. H. Lee, A. Matsumoto, M. Yoshida, and O. Simamura, *Chem. Lett.*, 951 (1974).

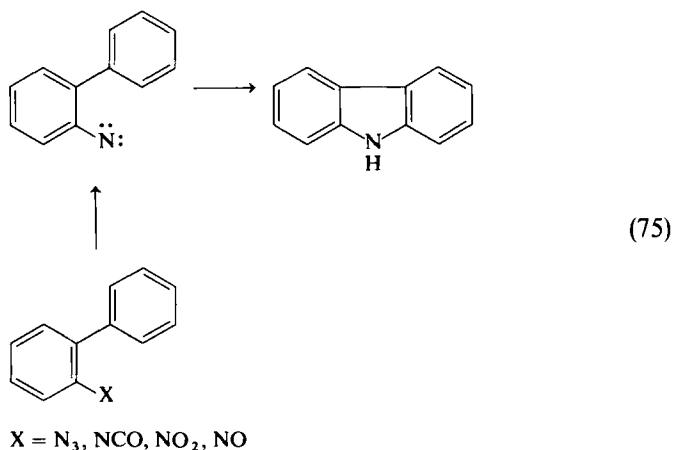
²⁹⁹ V. M. Colburn, B. Iddon, H. Suschitzky, and P. T. Gallagher, *Chem. Commun.*, 453 (1978).

³⁰⁰ P. Spagnolo, A. Tundo, and P. Zanirato, *J. Org. Chem.* **43**, 2508 (1978).

³⁰¹ J. S. Swenton, T. J. Ikeler, and G. LeRoy Smyser, *J. Org. Chem.* **38**, 1157 (1973); J. S. Swenton, T. J. Ikeler, and B. H. Williams, *J. Am. Chem. Soc.* **92**, 3103 (1970).

³⁰² F.-P. Tsui, T. M. Vogel, and G. Zon, *J. Org. Chem.* **40**, 761 (1975).

it was shown quite clearly by Swenton *et al.*³⁰¹ that it is the singlet nitrene which cyclizes to carbazole; the triplet gives amine or azobiphenyl.



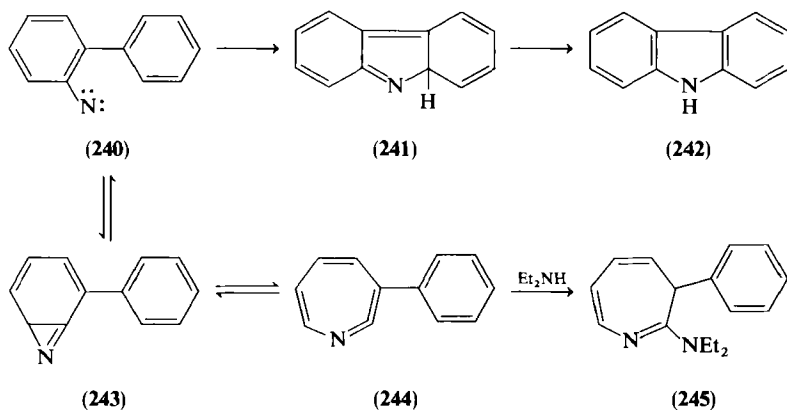
Lehmann and Berry³⁰³ reported a flash photolysis study of the carbazole formation from 2-azidobiphenyl in the gas phase and in solution. The rate constant for cyclization of the nitrene was measured in solution at 300 K as $2.18 \times 10^3 \text{ sec}^{-1}$, and an activation enthalpy of $11.46 \pm 0.76 \text{ kcal/mol}$ was derived. The rate in the gas phase at 75°C was unmeasurably fast (i.e., $\geq 1.4 \times 10^6 \text{ sec}^{-1}$). It was concluded that a singlet nitrene was first formed, but that it was the *triplet* that underwent cyclization.

However, Sundberg *et al.*^{304,305} demonstrated that *two* intermediates must be formed from the photolytically generated nitrene **240**. These were supposed to be the immediate carbazole precursor **241**, and the azirine **243** (Scheme 47) because part of the nitrenes could be trapped with diethylamine, giving **245**. In conformity with the discussion in Sections VIII,A–C we have added the azacycloheptatetraene **244** in Scheme 47. Since the trapping reaction (to **245**) was found to be a factor $\sim 10^2$ faster than carbazole formation, but the formation of **242** could not be completely suppressed, **241** was assumed to be the nontrappable intermediate. It was also found³⁰⁴ that the deoxygenation of 2-nitrosobiphenyl proceeded in a similar manner, and that a similar product ratio (**242**:**245**) resulted. Therefore, a free nitrene appears to be involved in this reaction also. A more detailed flash-photolytic study³⁰⁵ *excluded* the triplet nitrene **240** as a principal carbazole precursor. The nature of the observable transient is still unclear, however.

³⁰³ P. A. Lehmann and R. S. Berry, *J. Am. Chem. Soc.* **95**, 8614 (1973).

³⁰⁴ R. J. Sundberg and R. W. Heintzelman, *J. Org. Chem.* **39**, 2546 (1974).

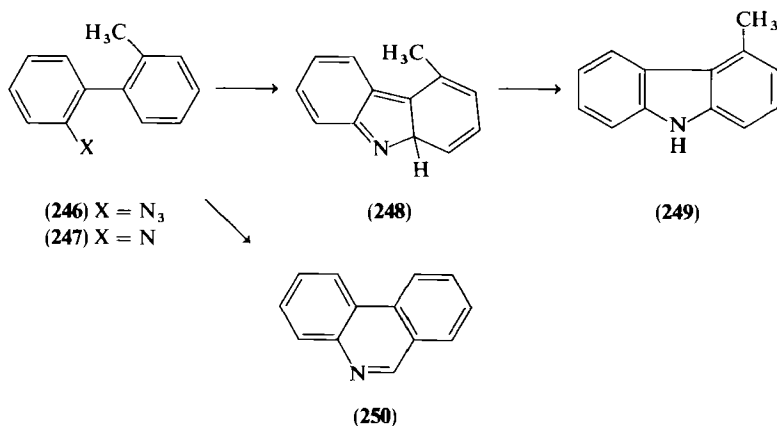
³⁰⁵ R. J. Sundberg, D. W. Gillespie, and B. A. DeGraff, *J. Am. Chem. Soc.* **97**, 6193 (1975).



SCHEME 47

Meth-Cohn and co-workers derived strong chemical support for the singlet nitrene-carbazole pathway from a study of the thermolysis and photolysis of the azide **246**.³⁰⁶ Here, the nitrene **247** has two intramolecular pathways open to it, namely, formation of carbazole (**249**) or phenanthridine (**250**) apart from intermolecular reactions leading to amine and azo compound (Scheme 48).

Their findings, using varied temperature, singlet-stabilizing solvents, heavy-atom solvents, direct and triplet-sensitized photolysis, and addition of pyrene (a singlet sensitizer and triplet quencher) led to the conclusion

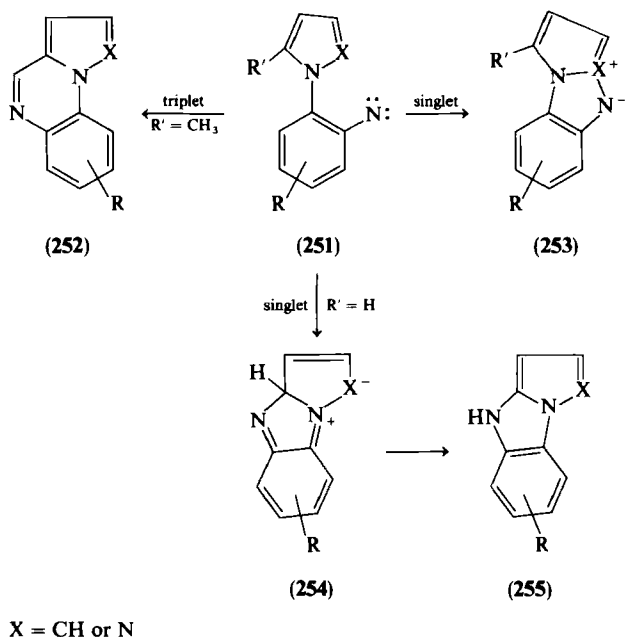


SCHEME 48

³⁰⁶ J. M. Lindley, I. M. McRobbie, O. Meth-Cohn, and H. Suschitzky, *J. C. S. Perkin I*, 2194 (1977).

that carbazole is derived from a singlet nitrene; phenanthridine, amine, and azo compound from the triplet. Direct photolysis gave about a 9:1 ratio of singlet to triplet nitrene in accord with the findings of Reiser and Leyshon.¹⁷

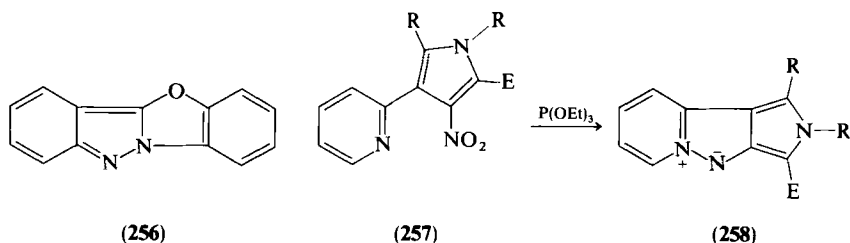
The formulation of these reactions as electrocyclic processes leading initially to **241** and **248** nicely explains why such reactions are inefficient with five-membered heterocyclic rings (Scheme 49).^{306,307} Such nitrenes (**251**) attack methyl groups in triplet reactions, and give the mesoionic heterocycles **253** ($X = N$) in singlet reactions. The latter are favored by electron-withdrawing substituents R, which increase the electrophilicity of the nitrene. Cyclization onto carbon, as in **255**, is rarely observed, and this is ascribed to the necessity of forming the nonaromatic zwitterionic intermediate **254**. Further aspects of this work have been reviewed, including cyclizations as in Scheme 49 where the heterocyclic ring is replaced by 2-furyl, 2-thienyl (no cyclization onto S), 2-thiazolyl, 2-benzimidazolyl, 2-pyridyl, 2-indazolyl, and 1-indazolyl.¹²



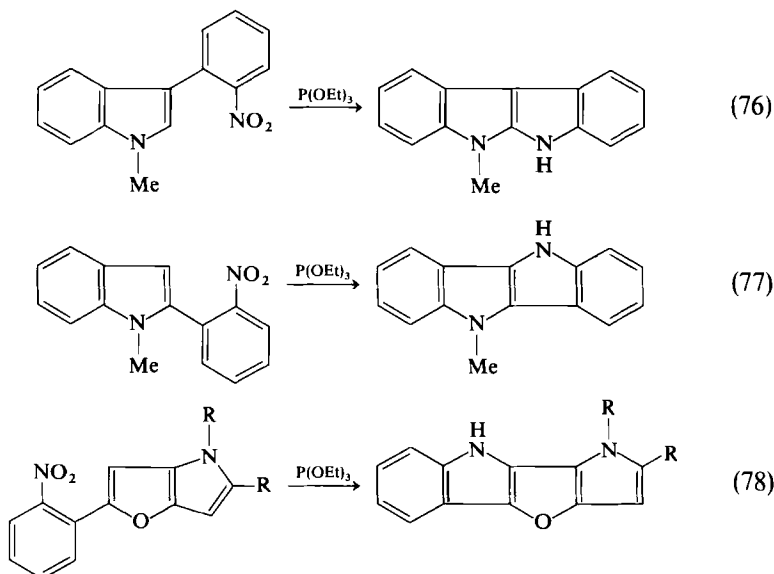
SCHEME 49

³⁰⁷ I. M. McRobbie, O. Meth-Cohn, and H. Suschitzky, *Tetrahedron Lett.*, 925 (1976); J. M. Lindley, I. M. McRobbie, O. Meth-Cohn, and H. Suschitzky, *J. C. S. Perkin I*, 982 (1980).

The attack on an *o*-(2-benzoxazolyl) substituent similarly occurs on nitrogen, giving the benzoxazoloindazole system **256**.³⁰⁸ The rings between which cyclization is to take place can also be interchanged, as in the reductive cyclization of the pyrrole **257** onto a pyridine ring, giving **258**.³⁰⁹



The cyclization with an *o*-(1-pyrrolyl) substituent (Scheme 49, X = CH) gives a pyrroloimidazole (**255**, X = CH).³⁰⁶ Related cyclizations onto *o*-(2- or 3-indolyl) give pyrrolopyrroles (Eqs. 76–77).³¹⁰ The reaction is apparently of almost unlimited versatility (e.g., Eq. 78).³¹¹



As mentioned in Section VIII.G, addition to the azo linkage is a nonnitrene process. The bis-azido compound **259** decomposes in two stages, the second

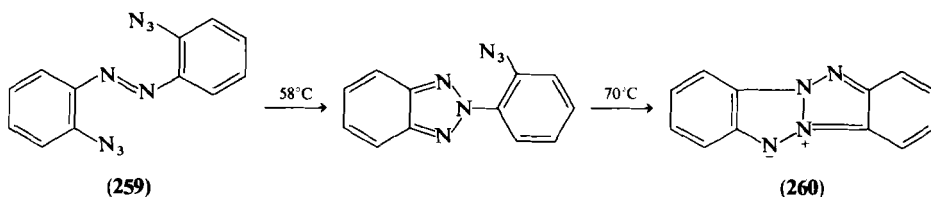
³⁰⁸ G. S. Reddy and K. K. Reddy, *Indian J. Chem., Sect. B* **15**, 84 (1977).

³⁰⁹ K. T. Potts, S. K. Datta, and J. L. Marshall, *J. Org. Chem.* **44**, 622 (1979).

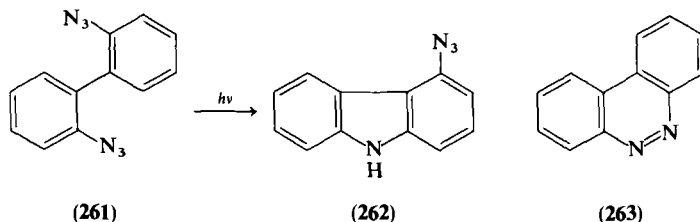
³¹⁰ A. H. Jackson, D. N. Johnston, and P. V. R. Shannon, *Chem. Commun.*, 911 (1975).

³¹¹ A. Krutosikova, J. Kovac, M. Dandarova, and M. Veverka, *Collect. Czech. Chem. Commun.* **44**, 1805 (1979).

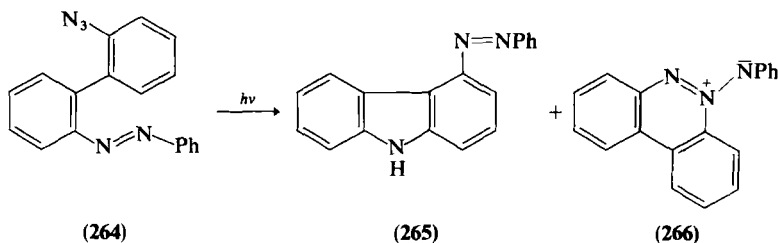
one being a nitrene process, which gives the interesting triazolotriazole **260**.³¹²



Another type of diazide **(261)** gives predominantly the normal carbazole **262** on photolysis at room temperature; at 77 K in hexane, however, the nitrene is trapped by the second azido group, giving **263** in 98% yield.³¹³



The *o*-azo-*o'*-azidobiphenyl **264** is trapped in a similar manner, giving both the carbazole **265** (10–15%) and the azimine **266** (35–40%).³¹⁴



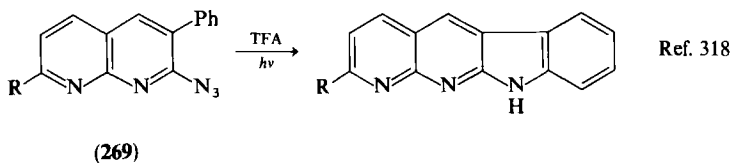
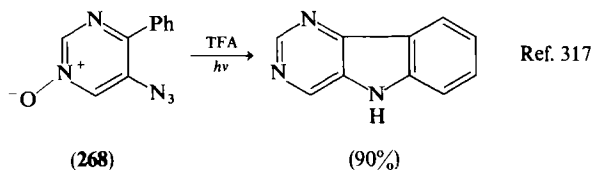
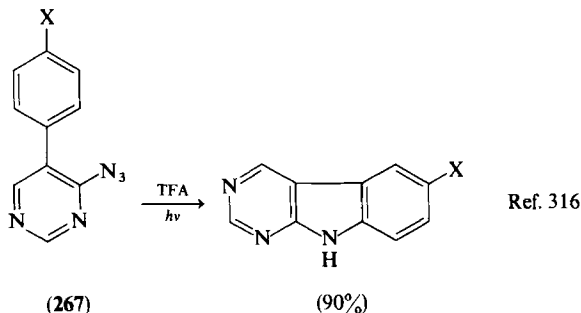
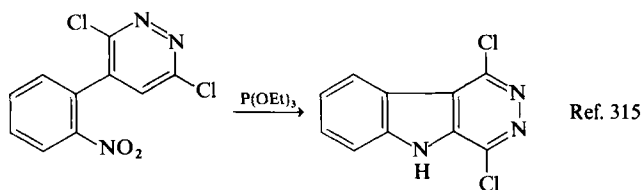
Examples of cyclization of aryl nitrenes onto neighboring six-membered heterocycles, and of heterocyclic nitrenes onto aryl rings, are given in Scheme 50a and b.^{315–321} Numerous other such reactions have been reviewed by Kametani *et al.*⁹

³¹² R. A. Carboni and J. E. Castle, *J. Am. Chem. Soc.* **84**, 2453 (1962); R. A. Carboni, J. C. Kauer, J. E. Castle, and H. E. Simmons, *ibid.* **89**, 2618 (1967); J. H. Hall, J. G. Stephanie, and D. K. Nordstrom, *J. Org. Chem.* **33**, 2951 (1968).

³¹³ A. Yabe and K. Honda, *Tetrahedron Lett.*, 1079 (1975).

³¹⁴ P. Spagnolo, A. Tundo, and P. Zanirato, *J. Org. Chem.* **42**, 292 (1977).

³¹⁵ T. Kurihara, E. Okada, and M. Akagi, *Yakugaku Zasshi* **92**, 1557 (1972) [*CA* **78**, 58335 (1973)].



SCHEME 50a

Compounds like **267** and **269** exist as the valence tautomeric tetrazoles in the solid state, but (in part) as the azides shown in trifluoroacetic acid.^{316,318,322-324} The vastly improved yields of carbazole-type products

³¹⁶ J. A. Hyatt and J. S. Swenton, *J. Heterocycl. Chem.* **9**, 409 (1972); *J. Org. Chem.* **37**, 3216 (1972).

³¹⁷ V. F. Sedova, V. P. Krivopalov, and V. P. Mamaev, *Khim Geterotsikl. Soedin.*, 986 (1977).

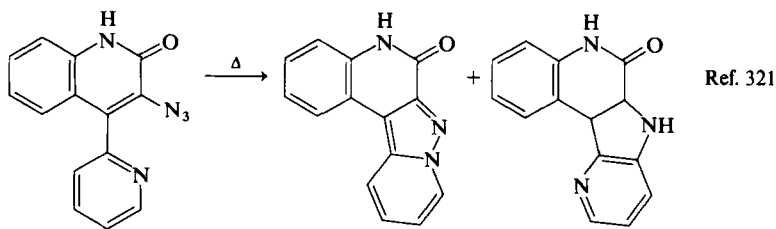
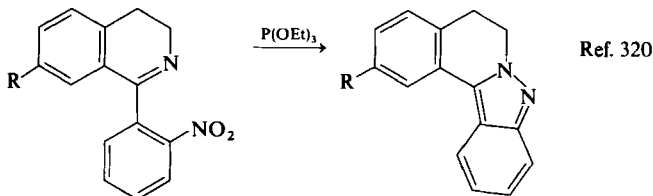
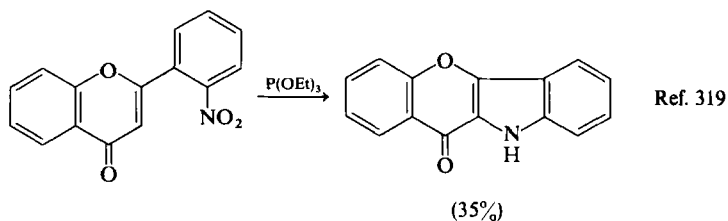
³¹⁸ A. DaSettimo, G. Primafore, V. Santerini, G. Biagi, and L. D'Amico, *J. Org. Chem.* **42**, 1725 (1977).

³¹⁹ F. M. Dean, C. Patampongse, and V. Podimuang, *J. C. S. Perkin I*, 583 (1974).

³²⁰ Y. P. Reddy, G. S. Reddy, and K. K. Reddy, *Indian J. Chem., Sect. B* **15**, 1133 (1977).

³²¹ R. Y. Ning, P. B. Madan, and L. H. Sternbach, *J. Org. Chem.* **38**, 3995 (1973).

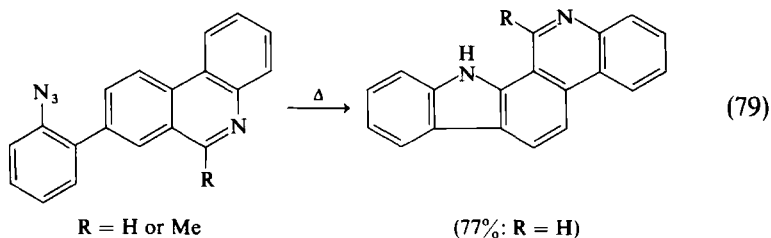
³²² C. Wentrup, *Tetrahedron* **26**, 4969 (1970).



SCHEME 50b

formed in trifluoroacetic acid are probably due to the fact that the heterocycles are protonated³²² in strongly acidic media. This renders the ensuing nitrenes more electrophilic, thereby increasing the rates of cyclization.

When a nitrene has a choice between two aromatic sites to attack, it will choose the one with the higher electron density, e.g., the 1-position in a naphthalene type of system. An example³²⁵ is shown in Eq. (79). The effect was also noted in Section VIII,C,5.

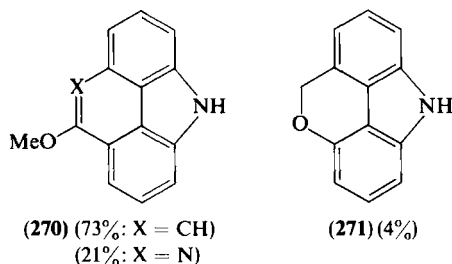


³²³ C. Thétaz, F. W. Wehrli, and C. Wentrup, *Helv. Chim. Acta* **59**, 259 (1976).

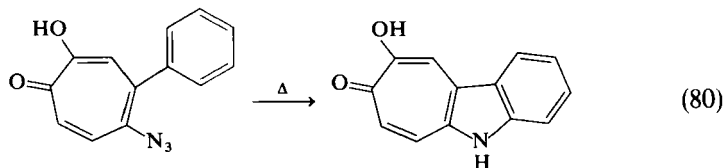
³²⁴ R. N. Butler, *Adv. Heterocycl. Chem.* **21**, 324 (1977).

³²⁵ L. H. Klemm, W. O. Johnson, and D. R. Olson, *J. Heterocycl. Chem.* **9**, 927 (1972).

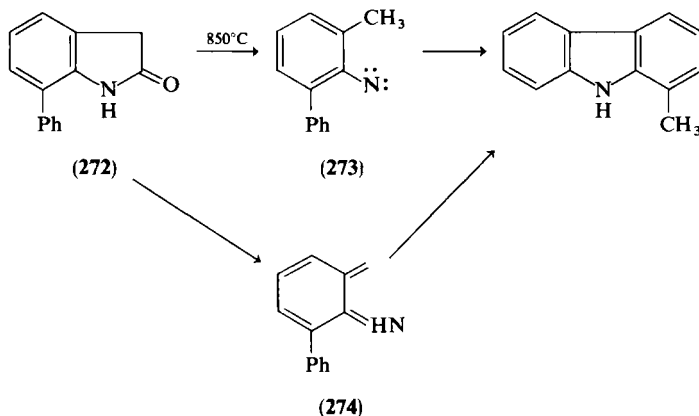
The tetracyclic ring systems **270** and **271** have been prepared by thermal cyclization (230–240°C) of the corresponding azides.³²⁶



The thermal cyclization of a tropolonoid azide has also been reported (Eq. 80).³²⁷



Finally, the unexpected formation of 1-methylcarbazole (43%) together with carbazole (11%) in the flash pyrolysis of **272** has been taken as evidence for the formation of a nitrene (**273**) although a CO extrusion to give the *o*-quinoid intermediate **274** seems more likely.³²⁸



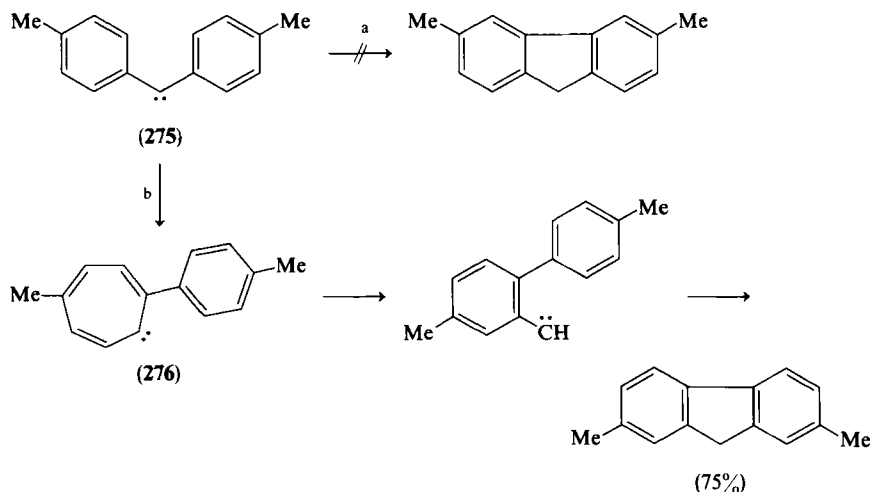
³²⁶ R. Kreher and W. Gerhardt, *Tetrahedron Lett.*, 3465 (1977).

³²⁷ T. Toda, H. Horino, and T. Nozoe, *Bull. Chem. Soc. Jpn.* **45**, 226 (1972).

³²⁸ R. F. C. Brown and M. Butcher, *Tetrahedron Lett.*, 667 (1971); *Aust. J. Chem.* **25**, 149 (1972).

2. By Carbene–Carbene or Carbene–Nitrene Rearrangement

The formation of fluorene from 2-biphenylcarbene is completely analogous to the carbazole formation described above. Contrary to earlier beliefs, the facile gas-phase rearrangement of diphenylcarbene to fluorene (Scheme 51) is *not* a direct process (path a).²⁰⁸ Other carbocyclic analogs of this reaction have been reported,^{10,329} and it has allowed the preparation of a number of heterocyclic compounds in high yields as well as a deeper understanding of the carbene–nitrene rearrangement.^{210,232}



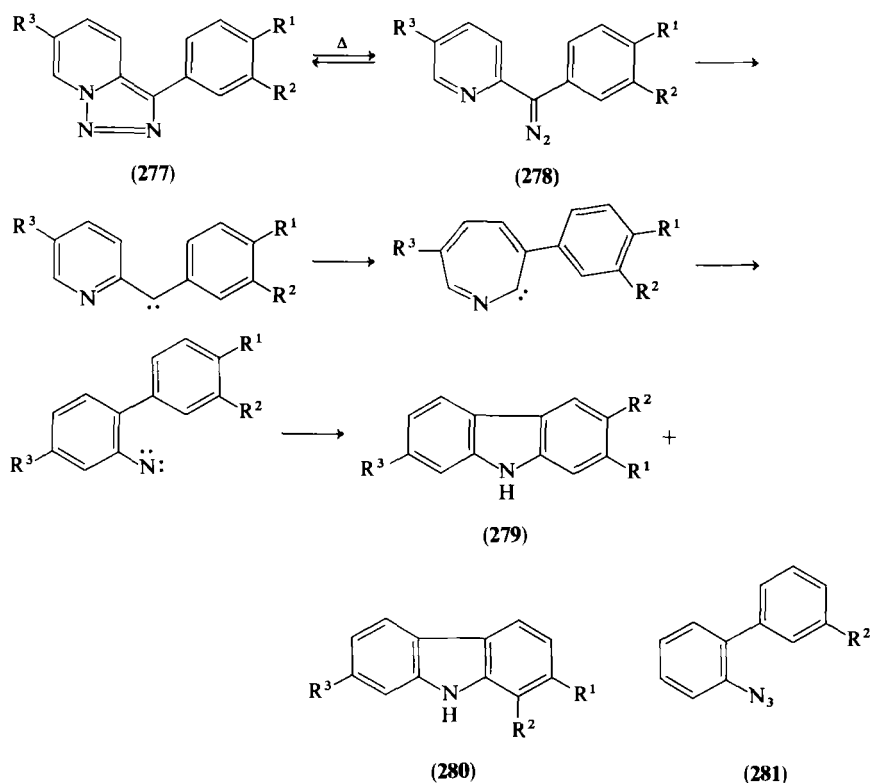
SCHEME 51

In this section the ring-expanded intermediates will mostly be designated as the carbenes (e.g., **276**) even though they may be better represented by, or in equilibrium with, cycloheptatetraenes (see Section VIII,A).

Flash thermolysis of 3-aryl[1,2,3]triazolo[1,5-*a*]pyridines (**277**) under mild conditions (380–500°C, $\sim 10^{-3}$ torr) affords carbazoles (**279**, **280**) in nearly quantitative yields.²³² The triazoles exist as the valence tautomeric diazo compounds **278** in the gas phase.¹⁸⁹ The substitution patterns in the products (**279** and **280**) demonstrate that the reactions take place exclusively by a carbene–nitrene rearrangement in which the pyridylcarbenes insert into the 2,3-bond in pyridine (Scheme 52).

The ratio of the two possible products (**279**, **280**) when $R^2 \neq H$ was the same as obtained from the corresponding 2-azidobiphenyls (**281**).

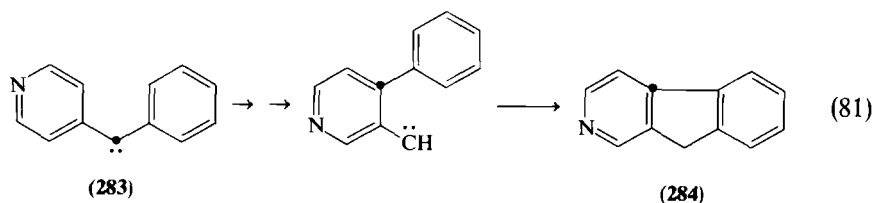
³²⁹ W. M. Jones, R. C. Joines, J. A. Myers, T. Mitsuhashi, K. E. Krajca, E. E. Waali, T. L. Davis, and A. B. Turner, *J. Am. Chem. Soc.* **95**, 826 (1973).

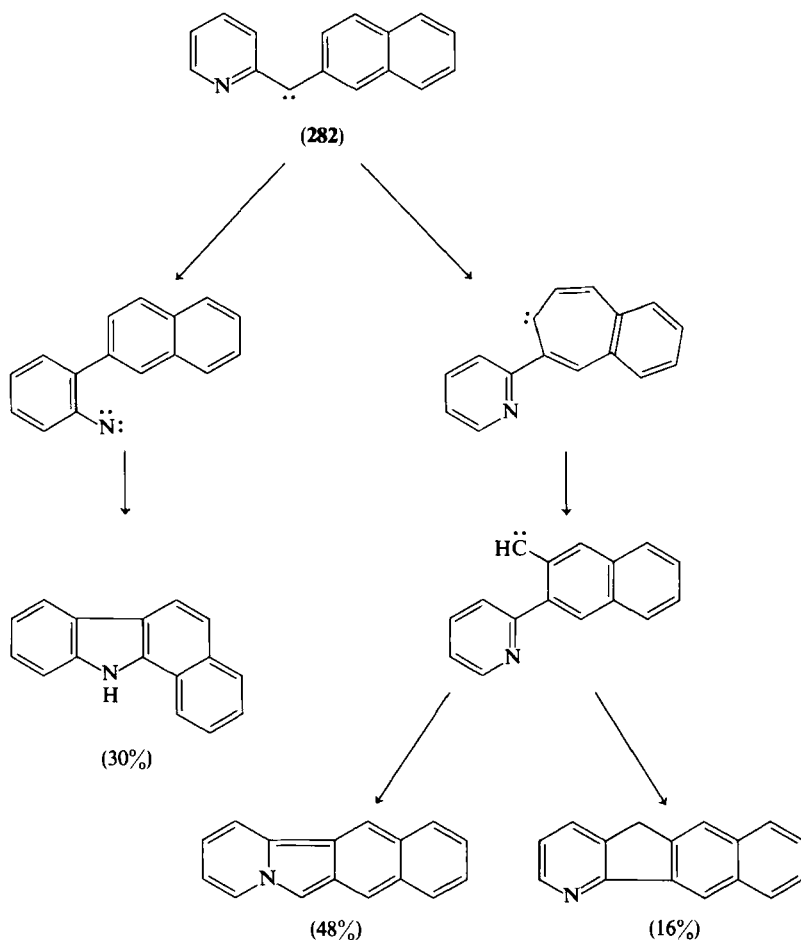


SCHEME 52

A deviation from the simple mechanism in Scheme 52 was observed with 2-pyridyl(2-naphthyl)carbene (**282**), from which a benzocarbazole, a pyrido[2,1-*a*]isoindole, and a benzindenopyridine were obtained (Scheme 53).²³²

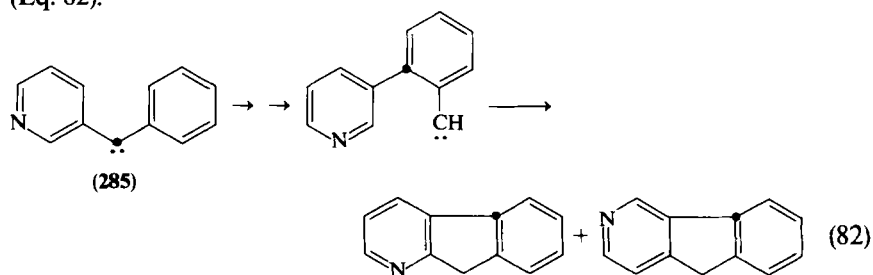
By pyrolysis of ¹⁴C-labeled phenyl(4-pyridyl)diazomethane it was shown that the carbene **283** rearranges predominantly via expansion into the 3,4-bond in pyridine (Eq. 81). The chemical yield of 2-azafluorene (**284**) was up to 70%.²³²





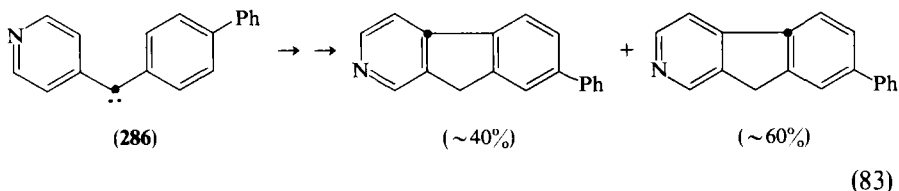
SCHEME 53

In contrast, ^{13}C -labeled phenyl(3-pyridyl)carbene (**285**) rearranged to a 1- and 3-azafluorene by virtually exclusive insertion into the benzene ring (Eq. 82).^{2,32}



These results led to the development of the theory of a synergic nucleophilic and electrophilic interaction between the carbenes and the aromatic rings.^{10,232} Briefly stated, a carbene will undergo ring expansion preferentially with the ring where an interaction between the filled carbene σ -orbital and the ring LUMO can occur simultaneously with an interaction between the vacant carbene p-orbital and the ring HOMO at the position ortho to the carbene. Accordingly, the 2- and 4-pyridylcarbenes expand preferentially into the pyridine ring (high LUMO coefficients in 2- and 4-positions; high HOMO coefficient in 3-position). The 3-pyridylcarbene **285** expands into the benzene ring because both HOMO and LUMO coefficients are low in the required pyridine positions. The 2-pyridyl-(2-naphthyl)carbene **282** expands in both directions because the LUMO energy of naphthalene is low, and the HOMO coefficient in the 1-position is high.

Further support for this theory was obtained from 4-pyridyl-(4-biphenyl)-carbene (**286**) which, due to the lowered benzenoid LUMO compared to **283**, underwent enhanced ring expansion into the benzene ring (Eq. 83).²¹⁰



A 2-pyrimidyl(phenyl)carbene (**287**) gives two products, the δ -carboline **288** (14%) by pyrimidine ring expansion, and the pyrimido[2,1-*a*]isoindole **289** (72%) by benzene ring expansion.²³² Compound **289** is the first example of this ring system (Scheme 54).

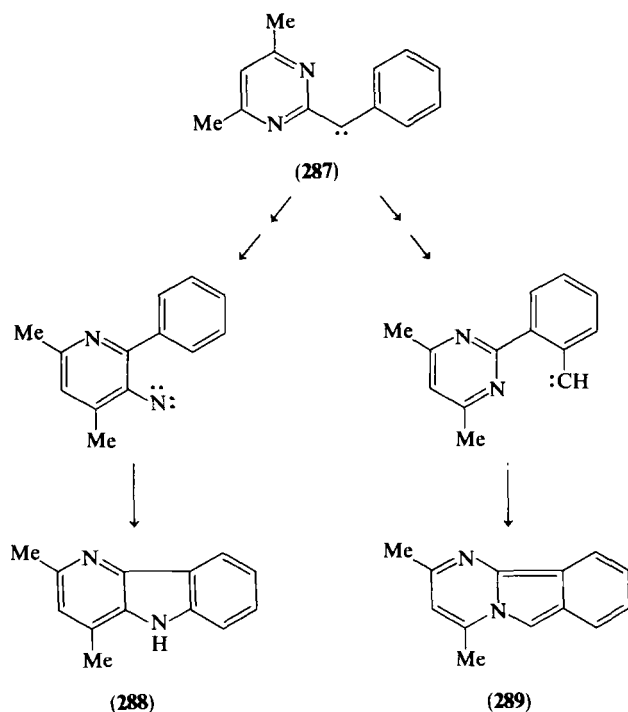
The fact that pyrimidine ring expansion does occur demonstrates that the unfavorable nonbonded interaction between the carbene σ -orbital and the nitrogen lone pair in the transition state is not a serious obstacle toward ring expansion.

Theoretical calculations^{218,330} support the contention that arylcarbenes will orient themselves in such a way as to increase the interaction between the σ -orbital and an electron-deficient ring.

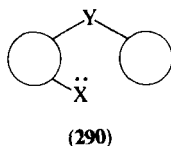
I. CYCLIZATION BETWEEN BRIDGED RINGS

This section considers cyclizations of arylnitrenes and carbenes onto another aromatic or heterocyclic ring of the type **290**, where the two rings are joined by a bridging group Y.

³³⁰ R. J. Miller, L. S. Yang, and H. Shechter, *J. Am. Chem. Soc.* **99**, 938 (1977).

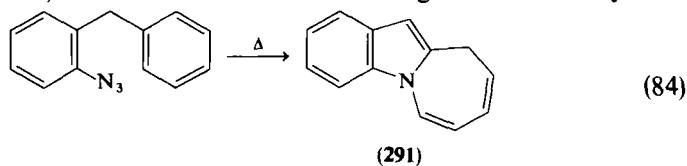


SCHEME 54



1. Methylene Bridging Group

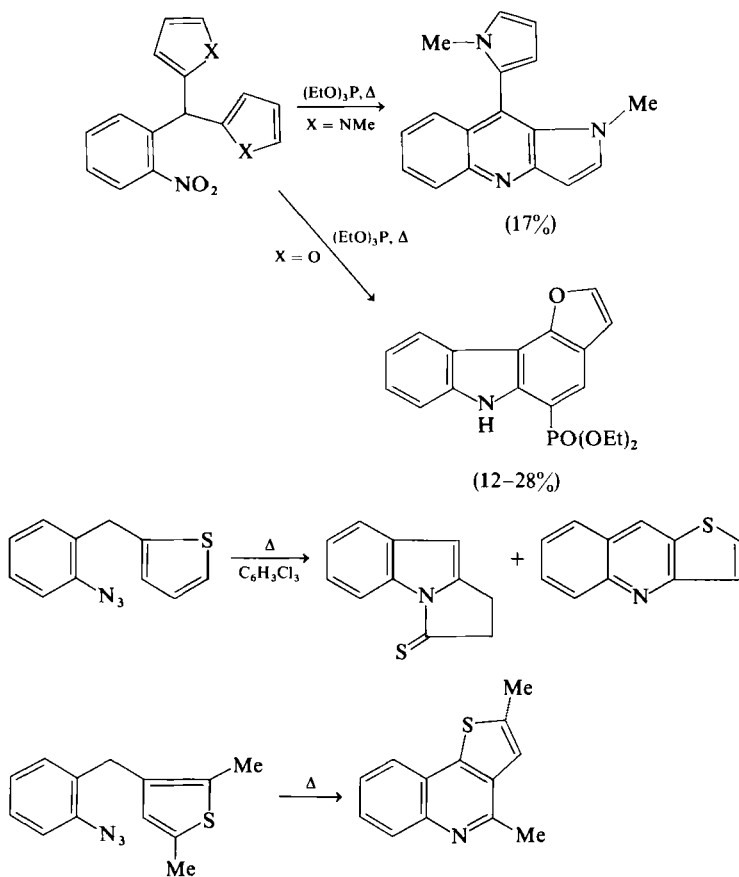
The most interesting case with $Y = CR_2$ is the formation of 10*H*-azepino-[1,2-*a*]indole (291) in 56% yield by liquid-phase pyrolysis of 2-azidodiphenylmethane (Eq. 84).^{331,332} The reaction is analogous to the very rare



³³¹ L. Krbecek and H. Takimoto, *J. Org. Chem.* **33**, 4286 (1968).

³³² G. R. Cliff, E. W. Collington, and G. Jones *J. Chem. Soc. C*, 1490 (1970).

inter-molecular insertion of arylnitrenes into benzene rings³³³ and presumably proceeds via a 7-azanocaradiene.^{331,332} Further examples include the related insertions into substituted phenyl rings,³³⁴ tetrahydronaphthalene rings,³³⁵ and one ring of the triphenylmethane system.³³⁶ The use of pyreryl,³³⁷ furyl,³³⁷ and thienyl^{338,339} rings led to substitution and rearrangement products (Scheme 55).



SCHEME 55

³³³ R. J. Sundberg and R. H. Smith, *Tetrahedron Lett.*, 267 (1971).

³³⁴ G. R. Cliff and G. Jones, *J. Chem. Soc. C*, 3418 (1971).

³³⁵ R. N. Carde and G. Jones, *J. C. S. Perkin I*, 2066 (1974).

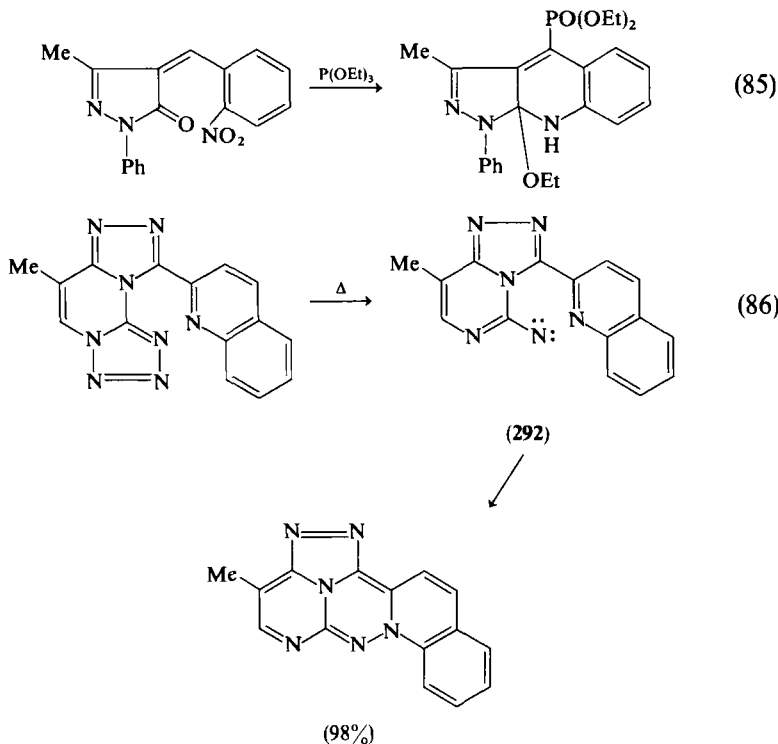
³³⁶ R. N. Carde, G. Jones, W. H. McKinley, and C. Price, *J. C. S. Perkin I*, 1211 (1978).

³³⁷ G. Jones and W. H. McKinley, *J. C. S. Perkin I*, 599 (1979).

³³⁸ G. R. Cliff, G. Jones, and J. McK. Woolard, *J. C. S. Perkin I*, 2072 (1974).

³³⁹ G. Jones, C. Keates, I. Kladko, and P. Radley, *Tetrahedron Lett.*, 1445 (1979).

Also formally belonging to this family of reactions are the reductive cyclizations shown in Eq. (85)³⁴⁰ and the cyclization of the pyrimidyl nitrene **292** onto the nitrogen atom of the remote quinoline ring (Eq. 86).³⁴¹



2. Sulfur Bridging Group

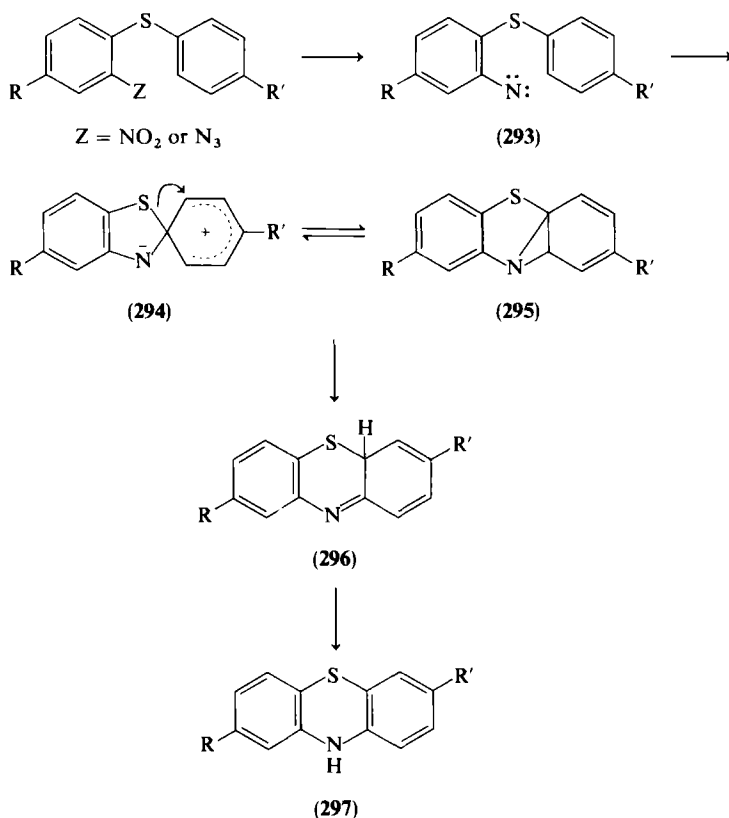
This case has been most thoroughly studied,⁸ and it was in this system that a new rearrangement was discovered^{342,343} which applies also in the cases to be discussed below where $\text{Y} = \text{O}$, NR , SO_2 , or CO . The general features of the rearrangement⁸ leading to phenothiazines (**297**) are summarized in Scheme 56. The nitrene **293** attacks the ring junction, forming the spirodiene intermediate **294**, possibly in equilibrium with the azanorcaradiene **295** (*vide infra*). The product is formed after a sigmatropic shift of sulfur

³⁴⁰ T. Nishiwaki, G. Fukuhara, and T. Takahashi, *J. C. S. Perkin I*, 1606 (1973).

³⁴¹ A. Könnecke, E. Lippmann, R. Dörre, and P. Lepom, *Tetrahedron Lett.*, 3687 (1978).

³⁴² M. Messer and D. Farge, *Bull. Soc. Chim. Fr.*, 2832 (1968).

³⁴³ J. I. G. Cadogan, S. Kulik, and M. J. Todd, *Chem. Commun.*, 736 (1968).



R = H or CH₃CO

R' = CF₃, Cl, CH₃O, CH₃, *t*-Bu, SCH₃, D

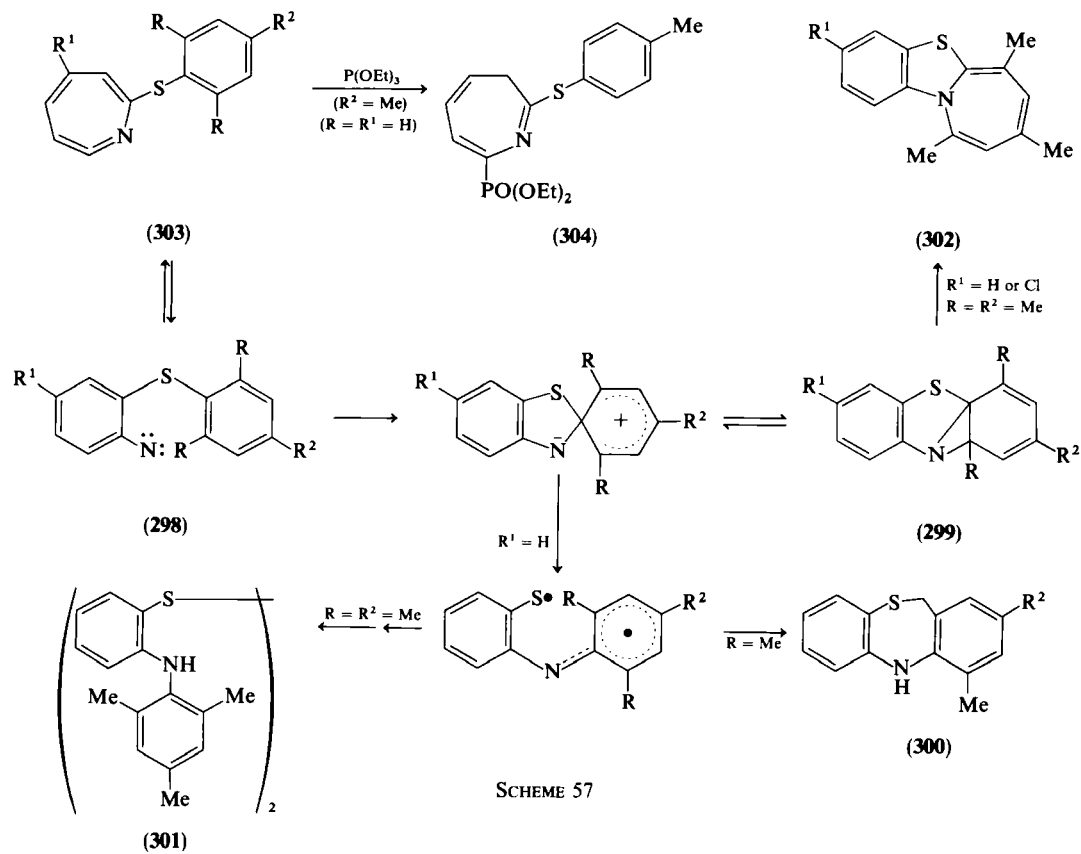
SCHEME 56

to give **296**. Complete transposition was also observed with a nitrene carrying a *S*-(1-naphthyl) group, but with a *S*-(2-naphthyl) group a mixture of rearranged and unrearranged product was formed (about 45% each),³⁴⁴ possibly due to the large HOMO coefficient in the 1-position of naphthalene, which facilitates a direct electrophilic attack of the nitrene.

Formation of thiazepines (**300**) occurs when the *S*-aryl chain carries *o*-methyl groups. Evidence for this rearrangement pathway (Scheme 57) comes from the substituent pattern in **300** and the isolation of the radical dimer **301**.³⁴⁵

³⁴⁴ M. Messer and D. Farge, *Bull. Soc. Chim. Fr.*, 4395 (1969).

³⁴⁵ J. I. G. Cadogan and S. Kulik, *J. Chem. Soc. C*, 2621 (1971).

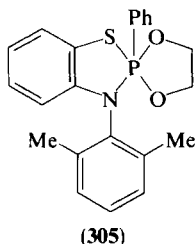


SCHEME 57

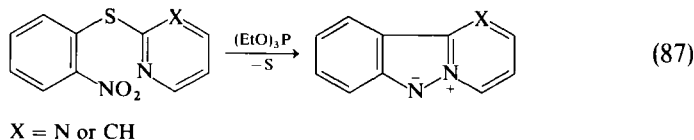
Moreover, evidence for the participation of the azanorcaradiene intermediate **299** (Scheme 57) has come from the isolation in up to 48% yield of azepinobenzothiazoles **302**, especially by photolysis of the azide starting material.³⁴⁶

The nitrenes in Schemes 56 and 57 must also be in preequilibrium with the corresponding bicyclic azirines and/or azacycloheptatetraenes **303** (Scheme 57) as demonstrated by the isolation of the azepine **304** in 2.5% yield in a deoxygenation reaction.³⁴⁷ Further examples of phenothiazine formation have been published.^{289,347}

As in all reactions using deoxygenation of nitro or nitroso compounds, there is a strong possibility that free nitrenes are not formed (see Section VIII,C,4).²⁶⁶ An interesting facet of the rearrangements shown in Schemes 56 and 57 is the isolation of thioaminophosphoranes (e.g., **305**; 73%) in deoxygenation reactions with tervalent phosphorus reagents.³⁴⁸



Attack on nitrogen in neighboring rings occurs in low yield (2–5%) and is accompanied by loss of sulfur (Eq. 87).³⁴⁷



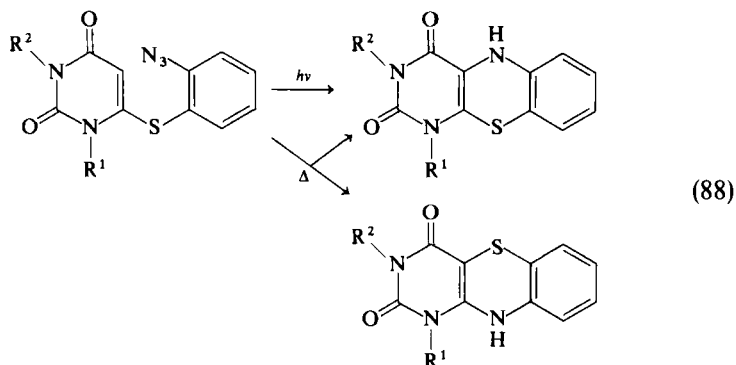
Attack on a vinylic bond in a pyrimidinedione occurs thermally with and without rearrangement, photochemically without, giving 10-thiaisoalloxazines (Eq. 88).³⁴⁹ Attack upon the 3-position in indole with spirodiene rearrangement has also been investigated.³¹⁰

³⁴⁶ I. M. McRobbie, O. Meth-Cohn, and H. Suschitzky, *J. Chem. Res. (S)*, 17 (1977); *J. Chem. Res. (M)*, 434 (1977).

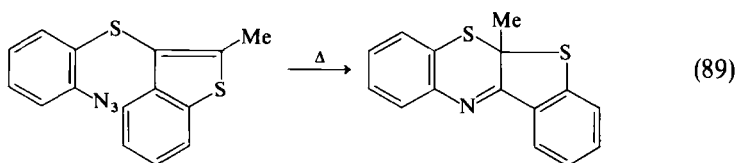
³⁴⁷ J. I. G. Cadogan and B. S. Tait, *J. C. S. Perkin I*, 2396 (1975).

³⁴⁸ J. I. G. Cadogan, R. O. Gould, and N. J. Tweddle, *Chem. Commun.*, 773 (1975).

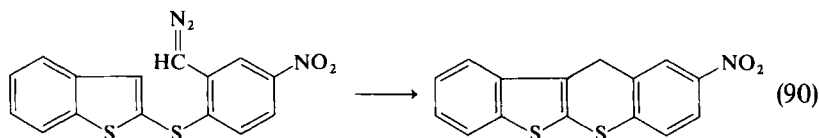
³⁴⁹ T. Hiramitsu and Y. Maki, *Chem. Commun.*, 557 (1977).



Cyclizations onto neighboring thiophene rings can lead to thienothiazines (Eq. 89)¹² although further rearrangements of the intermediates of type **294** often accompany such reactions.³⁵⁰



Little is known of related carbene reactions. The insertion shown in Eq. (90) proceeds without rearrangement.³⁵¹



3. O, N, SO₂, or CO Bridging Groups

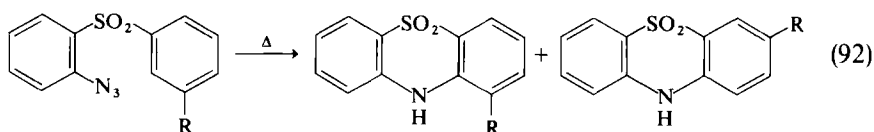
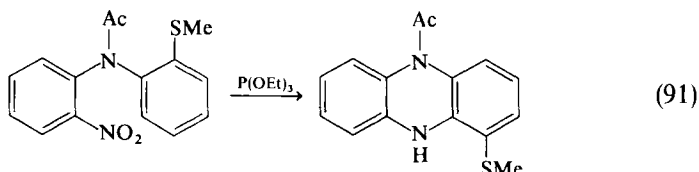
The ethers **290** (Y = O) behave in a manner quite similar to the thioethers giving phenoxazines, 1,4-oxazepines, and oxyaminophosphoranes (O in place of S in **297**, **300**, and **305**).^{8,352}

³⁵⁰ J. M. Lindley, O. Meth-Cohn, and H. Suschitzky, *J. C. S. Perkin I*, 1198 (1978).

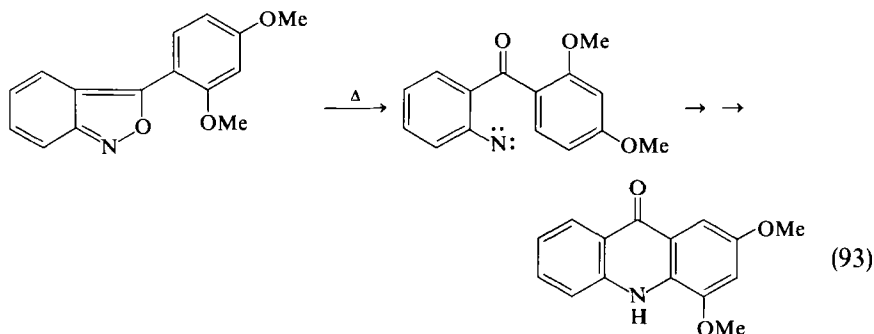
³⁵¹ B. Iddon, H. Suschitzky, D. S. Taylor, and K. E. Chippendale, *J. C. S. Perkin I*, 2500 (1974).

³⁵² J. I. G. Cadogan, D. S. B. Grace, P. K. K. Lim, and B. S. Tait, *J. C. S. Perkin I*, 2376 (1975); J. I. G. Cadogan, R. O. Gould, S. E. B. Gould, P. A. Sadler, S. J. Swire, and B. S. Tait, *ibid.*, 2392.

The amine analogs (Eq. 91) also react by rearrangement,³⁵³ whereas the sulfone (Eq. 92) gives a mixture of "rearranged" and "unrearranged" products.³⁵⁴



As mentioned above (Section VIII,C,2), anthranils open photolytically to nitrenes, which can be trapped in the form of azepines. Thermolysis, in contrast, leads to acridones, and a spirodiene rearrangement of the type shown in Scheme 56 was found to apply in this case also (Eq.93).³⁵⁵



An interesting application of this reaction, using an imidazole side chain (Scheme 58) gave mainly the "rearranged" imidazopyrimidine **306** together with 3% of the product of direct cyclization onto nitrogen (**307**).³⁵⁶

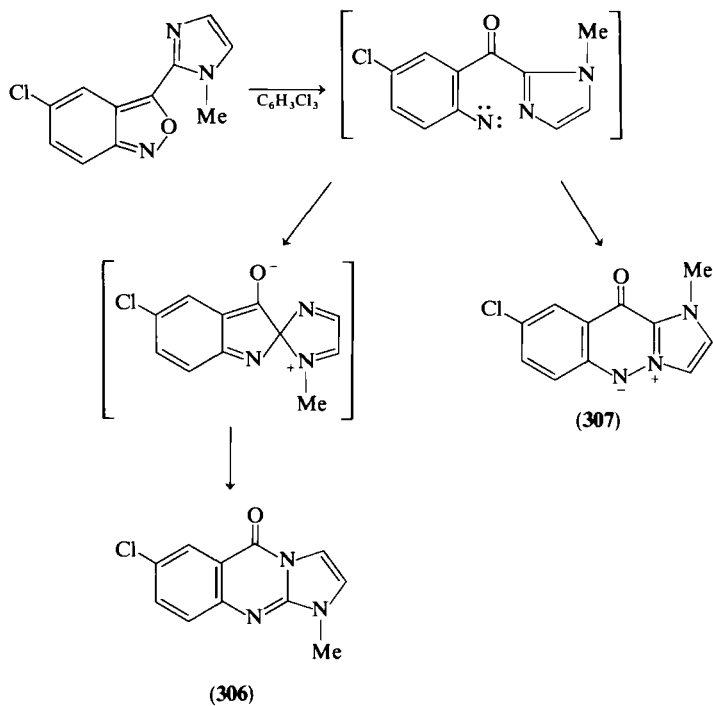
Recently, Smalley *et al.*²⁸⁸ have shown that a related rearrangement occurs even with a styryl substituent in place of an aromatic ring. An intermediate like **308** (Scheme 59) accounts for the products **309** and **310**.

³⁵³ Y. Maki, T. Hosokami, and M. Suzuki, *Tetrahedron Lett.*, 3509 (1971).

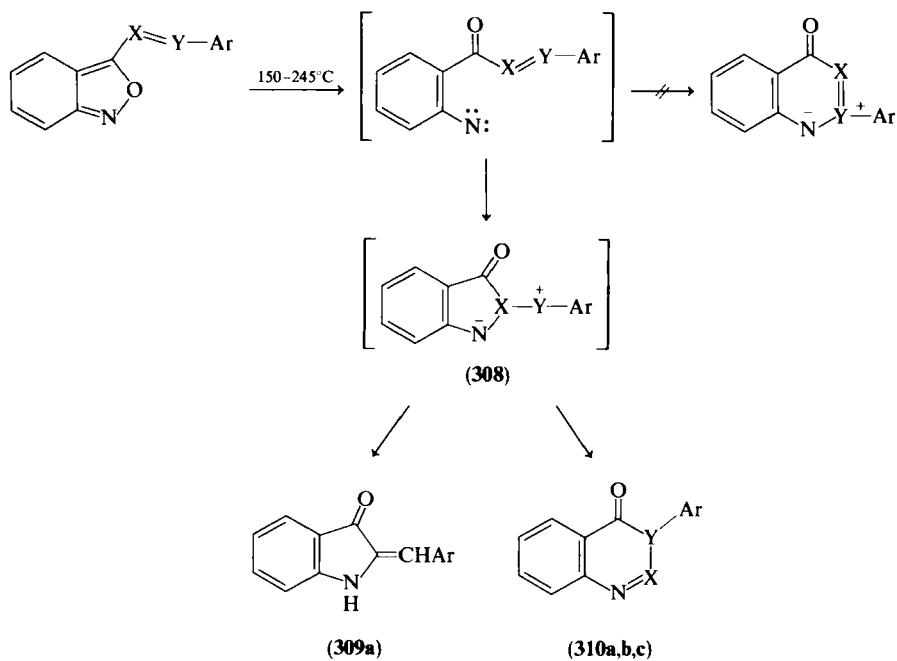
³⁵⁴ J. I. G. Cadogan, J. N. Done, G. Lunn, and P. K. K. Lim, *J. C. S. Perkin I*, 1749 (1976).

³⁵⁵ R. Kwok and P. Pranc, *J. Org. Chem.* **33**, 2880 (1968).

³⁵⁶ R. Y. Ning, J. F. Blount, P. B. Madan, and R. I. Fryer, *J. Org. Chem.* **42**, 1791 (1977).



SCHEME 58



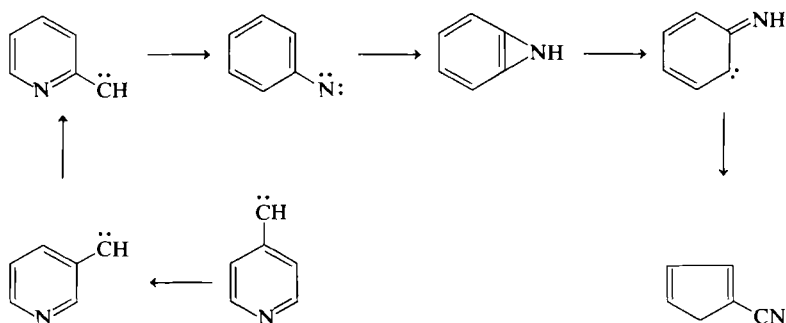
- (a) $\text{X}=\text{Y} = \text{CH}=\text{CH}$
- (b) $\text{X}=\text{Y} = \text{CH}=\text{N}$
- (c) $\text{X}=\text{Y} = \text{N}=\text{N}$

SCHEME 59

J. ULTIMATE FATE: RING CONTRACTION OR RING OPENING

When no other inter- or intramolecular reaction pathway is available for an arylnitrene, it will undergo ring contraction to a five-membered ring system, and sometimes also ring opening.^{10,13} Such reaction conditions are best realized using flash thermolysis at reduced pressure. Phenylcarbene undergoes ring contraction to fulvenallene (vinylidenecyclopentadiene) via ring expansion to cycloheptatrienylidene.^{194,357} A heteroarylcarbene will normally rearrange to the isomeric arylnitrene which then undergoes ring contraction. These reactions are summarized below. More detailed discussions of the reaction mechanisms are available.^{10,13}

Labeling experiments showed that 1*H*-benzazirines rather than azacycloheptatrienylidenes (azacycloheptatetraenes) are the immediate precursors of the ring contraction products from the three pyridylcarbenes, phenylnitrene, and naphthylnitrenes²⁰³ (Scheme 60; for the carbene–nitrene interconversions, see Section VIII,A). The reaction thus joins the same path as when starting from benzotriazole or isatin (Section III, Scheme 16). The rearrangement of pentafluorophenylnitrene to pentafluorocyclopentadiene-carbonitrile³⁵⁸ may take a different path. This must also be true of the facile ring contraction in azidobenzene tricarbonylmanganese cations to (cyanocyclopentadienyl)tricarbonylmanganese complexes.³⁵⁹



SCHEME 60

Although the ring-contraction paths followed by phenylcarbene and phenylnitrene are different, it is noteworthy that the naphthylcarbenes take a course not without similarity to phenylnitrene: both ring expansion and

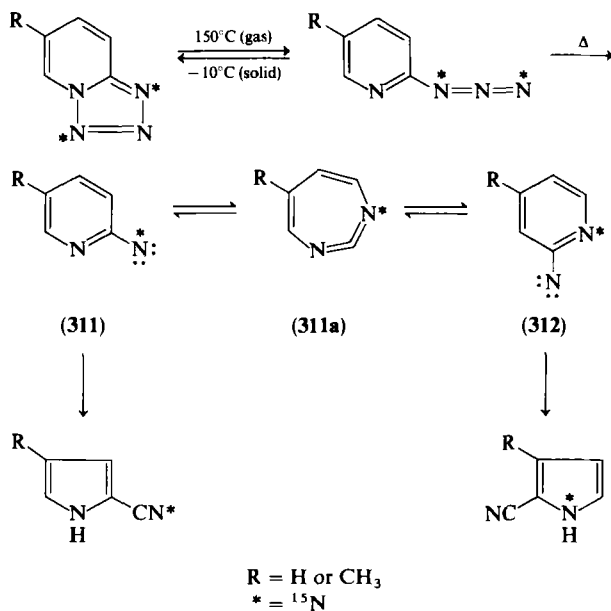
³⁵⁷ C. Wentrup, E. Wentrup-Byrne, and P. Müller, *Chem. Commun.*, 210 (1977).

³⁵⁸ B. Al-Saleh, R. E. Banks, M. G. Barlow, and J. C. Hornby, *J. Fluorine Chem.* **12**, 341 (1978); cf. R. E. Banks, M. G. Barlow, and N. D. Venayak, *Chem. Commun.*, 151 (1980).

³⁵⁹ G. A. Munro and P. L. Pauson, *J. Organomet. Chem.* **160**, 177 (1978).

ring contraction occur, but the major product (cyclobuta[*de*]naphthalene) is one of C—H insertion into the *peri* position (Eq. 69).

Labeling with substituents and with ^{15}N has established that pyridylnitrenes undergo 100% nitrene–nitrene interconversion prior to the formation of the final products, namely, cyanopyrroles (yield up to 85%), glutakonitriles (0–6%), and 2-aminopyridines (by hydrogen abstraction, 0–15%).³⁶⁰ A double labeling, using both a methyl group and ^{15}N , showed that the equilibrating nitrenes **311** and **312** contract independently, and that 1-cyanopyrroles *cannot* be formed as intermediates (Scheme 61).³⁶¹ The ring-expanded intermediate **311a** ($\text{R} = \text{H}$) was directly observable by IR spectroscopy at -196°C .^{222a}



SCHEME 61

Ring contraction in pyridylnitrenes formed by pyrolysis of pyrido[2,3-*a*]-[1,2,4]oxadiazol-2-ones has also been reported.³⁶²

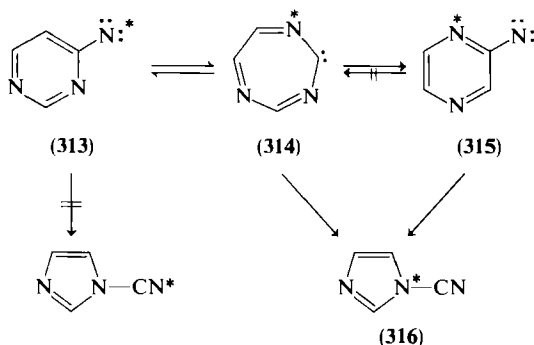
4-Pyrimidylnitrenes (**313**) undergo ring contraction after rearrangement, as shown by the complete label migration. In this case the products are 1-cyanoimidazoles (**316**) (contrast to the pyridylnitrenes), and the yields are

³⁶⁰ W. D. Crow and C. Wentrup, *Chem. Commun.*, 1387 (1969).

³⁶¹ R. Harder and C. Wentrup, *J. Am. Chem. Soc.* **98**, 1259 (1976).

³⁶² R. F. C. Brown and R. J. Smith, *Aust. J. Chem.* **25**, 607 (1972).

often quantitative.^{222,226,363} On the other hand, 2-pyrazinylnitrene (**315**) contracts *without* label migration,²²² and this last reaction takes place even in solution.³⁶⁴ It is most reasonable to assume that the 4-pyrimidyl nitrenes **313** ring expand to the cyclic carbene or carbodiimide **314** prior to ring contraction, whereas the pyrazinylnitrene **315** contracts directly (Scheme 62, see also Scheme 35).



SCHEME 62

It was also shown in this work³⁶⁴ that a previously postulated ring *expansion* in a pyrazinylnitrene³⁶⁵ was erroneous.

In the isomeric pair, 2-pyrimidyl nitrene (**317**) and 3-pyridazinylnitrene (**318**) there is no evidence for nitrene–nitrene interconversion.^{10,363,366} The former gives 1-cyanopyrazoles (**319**) in up to 62% yield; the latter undergoes ring opening, nitrogen extrusion, and formation of a mixture of C₄H₃N nitriles (Scheme 63).

Ring opening and/or ring contraction has been reported for 2-quinolyl nitrene,^{221,222,367} 4-quinazolinylnitrene,²²¹ 2-quinoxalinylnitrene,²²¹ and 9-phenanthridinylnitrene.^{221,222} Even the latter undergoes nitrene–nitrene interconversion prior to the formation of 4- and 9-cyanocarbazoles.^{222,222a}

2-Quinolylcarbene and 1-isoquinolylcarbene undergo carbene–nitrene rearrangement to 1-naphthyl nitrene and 2-naphthyl nitrene, respectively.^{10,202} Both 2- and 4-pyrimidylcarbenes and 2-pyrazinylcarbene isomerize to 3- and 4-pyridyl nitrenes, respectively, which then contract to cyanopyrroles.¹⁰ 2-Phenyl-4-quinazolylcarbene (**320**) does *not* rearrange to 2-phenyl-3-quinolyl nitrene (**322**), but undergoes ring contraction in very high yield to 2-phenyl-3-cyanoindole (**323**) via the cyclic ketenimine **321** (Scheme 64).^{13,223}

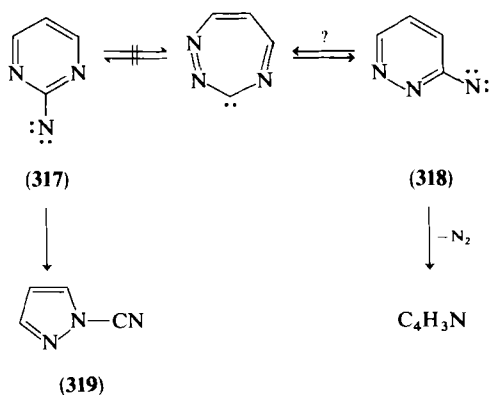
³⁶³ C. Wentrup and W. D. Crow, *Tetrahedron* **26**, 4915 (1970).

³⁶⁴ C. Wentrup, *Helv. Chim. Acta* **55**, 565 (1972).

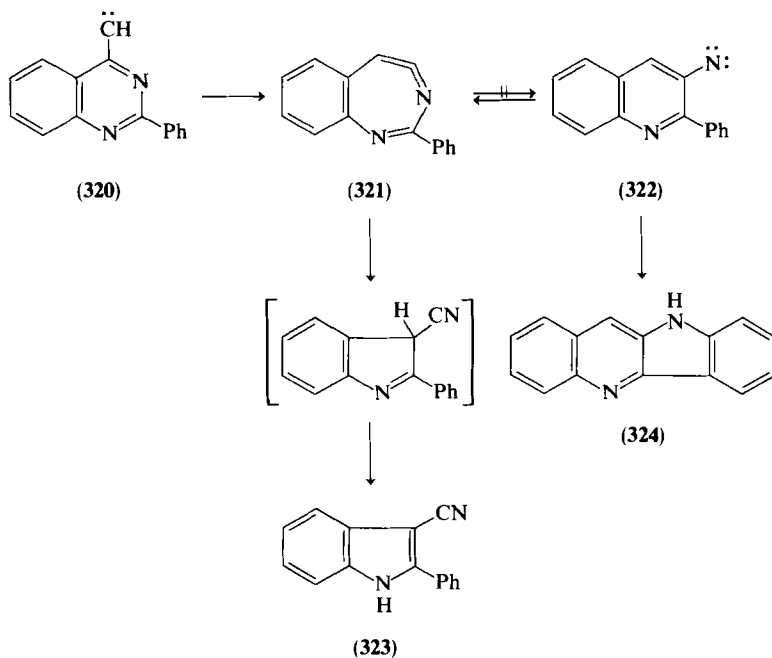
³⁶⁵ T. Sasaki, K. Kanematsu, and M. Murata, *J. Org. Chem.* **36**, 446 (1971).

³⁶⁶ C. Wentrup and W. D. Crow, *Tetrahedron* **27**, 361 (1971).

³⁶⁷ R. F. C. Brown, F. Irvine, and R. J. Smith, *Aust. J. Chem.* **26**, 2213 (1973).



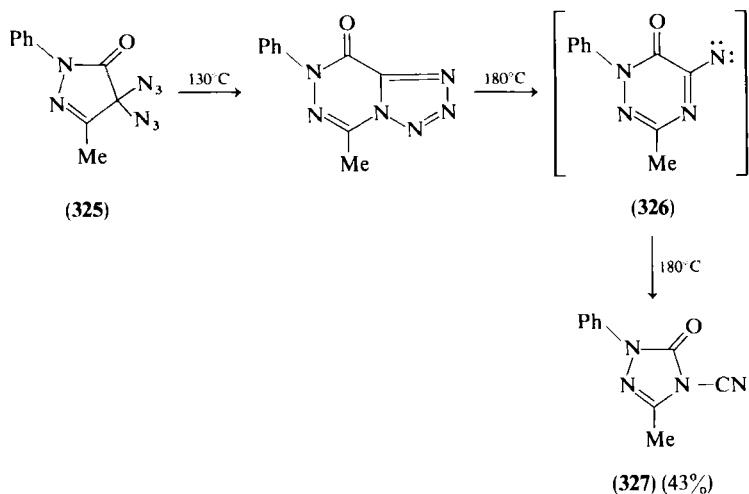
SCHEME 63



SCHEME 64

The nitrene **322**, generated by gas phase thermolysis of the corresponding azide, gave both the ring-contraction product **323** and the product of cyclization onto the phenyl ring (**324**).²²³

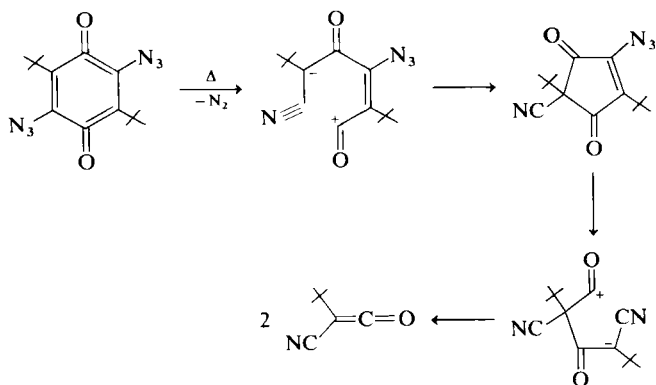
A nitrene (**326**) that may be regarded as an imidoynitrene rather than an aryl nitrene is formed in a two-stage solution-phase thermolysis of the diazide



SCHEME 65

325.³⁶⁸ It is not known whether the ring contraction to **327** is "direct" or proceeds via ring expansion (Scheme 65).

The consecutive ring openings and ring contractions in azidoquinones are formulated as zwitterionic reactions, not involving nitrenes (cf. Scheme 66).^{369,370} The latter account³⁷⁰ summarizes several examples of ring contraction in azidoquinones, -tropone, -azepinediones, -quinols, and related compounds.



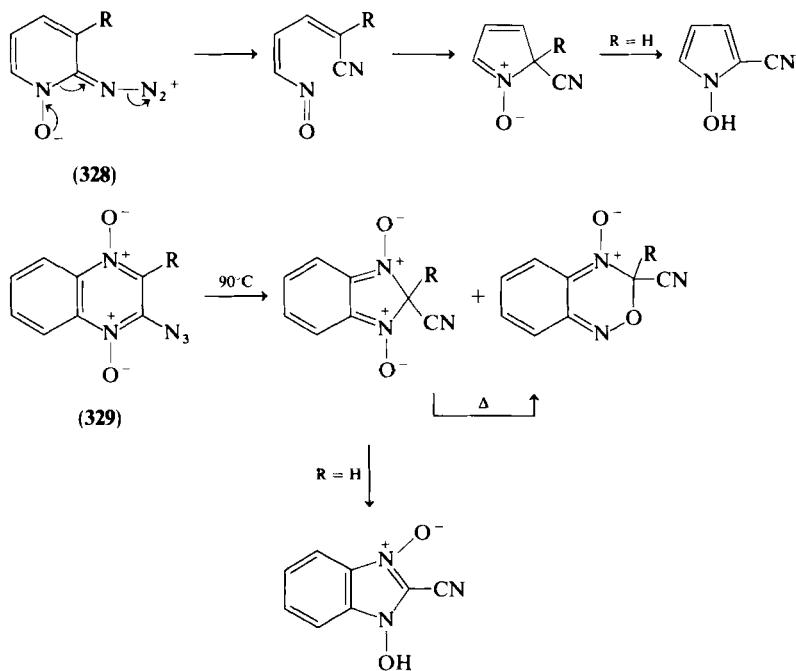
SCHEME 66

³⁶⁸ G. Landen and H. W. Moore, *Tetrahedron Lett.*, 2513 (1976).

³⁶⁹ H. W. Moore, *Chem. Soc. Rev.* **2**, 415 (1973).

³⁷⁰ H. W. Moore, *Acc. Chem. Res.* **12**, 125 (1979).

The ring contractions of 2-azidopyridine *N*-oxides (328) to 1-hydroxypyrrroles,³⁷¹ and of 2-azidoquinoxaline 1,4-dioxides (329)³⁷² (Scheme 67) are also believed to be assisted nonnitrene reactions, as symbolized in formula 328, because they generally take place in solution below 100°C.



SCHEME 67

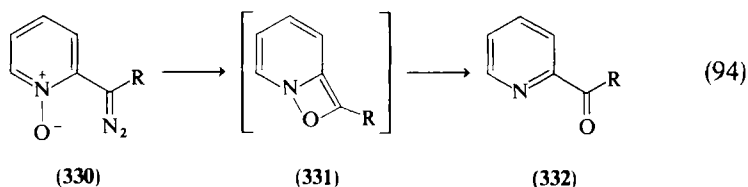
These reactions are very interesting from the point of view of synthesis of novel heterocyclic compounds. Analogs are not found in the isosteric carbenes, however. 2-Diazomethylpyridine *N*-oxides (330) give rise to 2-acylpyridines (332) by photolysis or thermolysis.^{373,374} In view of the surprisingly facile formation of cyclobuta[*de*]naphthalene from 1-naphthylcarbene (see Eq. 69) the intermediate 10 π -electron pyridooxazete 331 does not seem unreasonable (Eq. 94). Other pathways are possible too, however.²⁷³

³⁷¹ R. A. Abramovitch and B. W. Cue, *J. Org. Chem.* **38**, 173 (1973); *Heterocycles* **1**, 227 (1973); **2**, 297 (1974); *J. Am. Chem. Soc.* **98**, 1478 (1976).

³⁷² J. P. Dirlam, B. W. Cue, and K. J. Gombatz, *J. Org. Chem.* **43**, 76 (1978).

³⁷³ R. A. Abramovitch, C. S. Menon, M. Murata, and E. M. Smith, *Chem. Commun.*, 693 (1974).

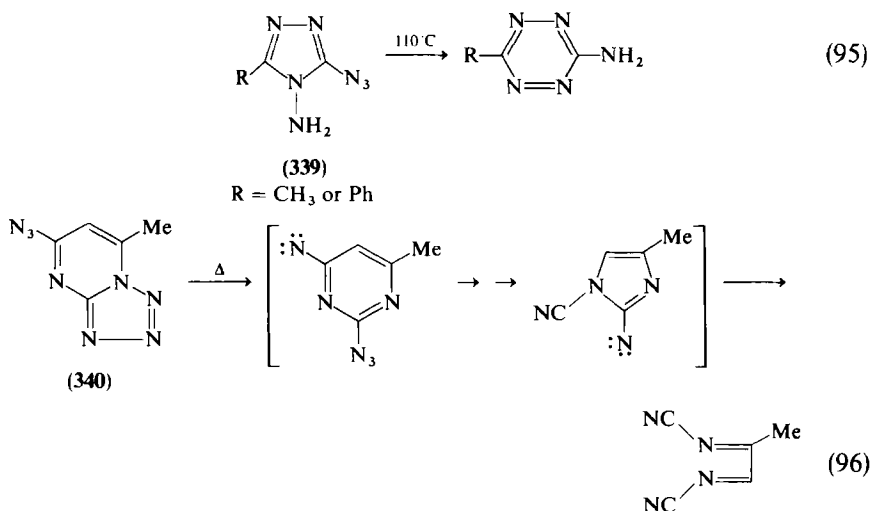
³⁷⁴ H. Güsten and E. F. Ullman, *Z. Naturforsch., Teil B* **31**, 1009 (1976).



IX. Five-Membered Heteroarylcarbenes and Heteroarylnitrenes

The most frequent reaction for the five-membered heteroarylcarbenes and -nitrenes appears to be ring opening. Smith *et al.*^{174,375,376} give a fascinating account of the 5-azido-1,2,3-triazole **333a** and other related systems which undergo ring opening to the nitriles **335** at 40–50°C. The surprising chemistry of **335** (e.g., formation of amines **336** by reduction) was first thought to indicate the presence of the singlet “nitrene” **334** in equilibrium with **335**,³⁷⁵ but the subsequent isolation of **337** showed that the amines are formed from open-chain compounds.³⁷⁶ More surprising is the formation of the azo compound **338b** purely by thermolysis of the nitrile **335b** (Scheme 68).^{375,376}

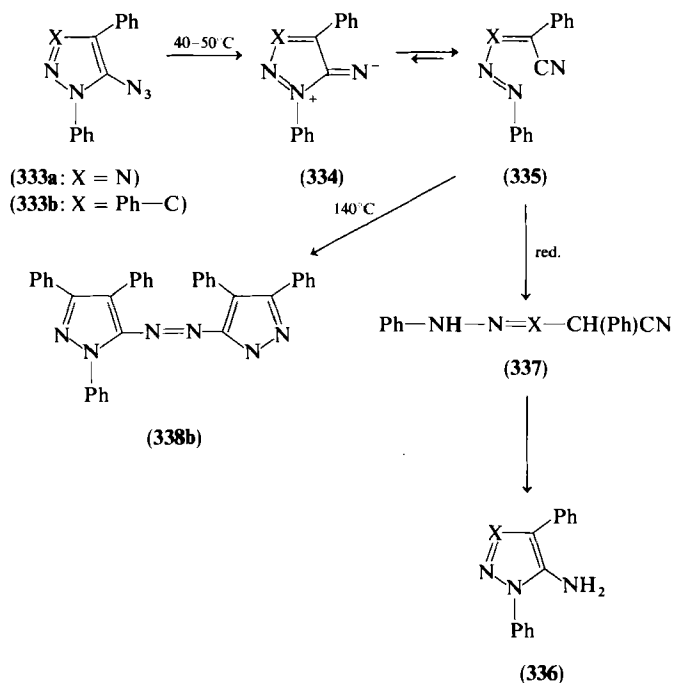
Similar ring opening reactions were postulated to account for the transformation of the azides **339** into tetrazines (Eq. 95),³⁷⁷ and for the transformation of the azidotetrazolopyrimidine **340** into a dicyanodiazabutadiene (Eq. 96).³²²



³⁷⁵ P. A. S. Smith, L. O. Krbecek, and W. Resemann, *J. Am. Chem. Soc.* **86**, 2025 (1964).

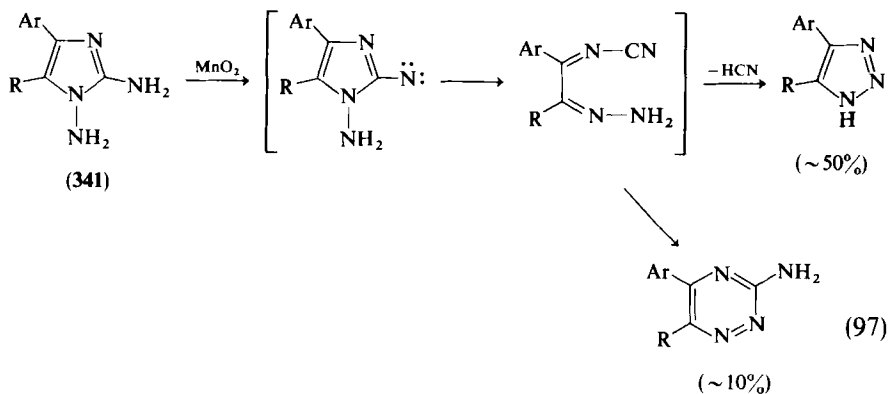
³⁷⁶ P. A. S. Smith, G. J. W. Breen, M. K. Hajek, and D. V. C. Awang, *J. Org. Chem.* **35**, 2215 (1970).

³⁷⁷ H. H. Takimoto and G. C. Denault, *Tetrahedron Lett.*, 5369 (1966).



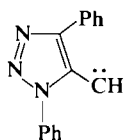
SCHEME 68

A 2-imidazolynitrene was also invoked to explain the products of oxidation of the diamine **341** (Eq. 97).³⁷⁸ The isomeric aminonitrene could also play a role in some of the reactions.³⁷⁸



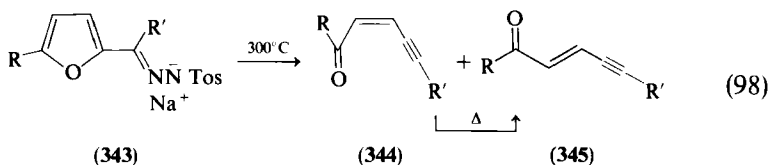
³⁷⁸ R. Hisada, M. Nakajima, and J.-P. Anselme, *Tetrahedron Lett.*, 903 (1976); M. Nakajima, R. Hisada, and J.-P. Anselme, *J. Org. Chem.* **43**, 2693 (1978).

The carbenes **342** (isosteric with **334**) do not undergo ring opening,³⁷⁹ but behave as typical electrophilic arylcarbenes in intermolecular reactions.³⁸⁰



(342)

Perhaps flash vacuum thermolysis of **342** should be tried, for the 2-furylcarbenes derived from **343** do give ring-opened acetylenes (**344**–**345**) in 20–60% yields under such conditions (Eq. 98).³⁸¹



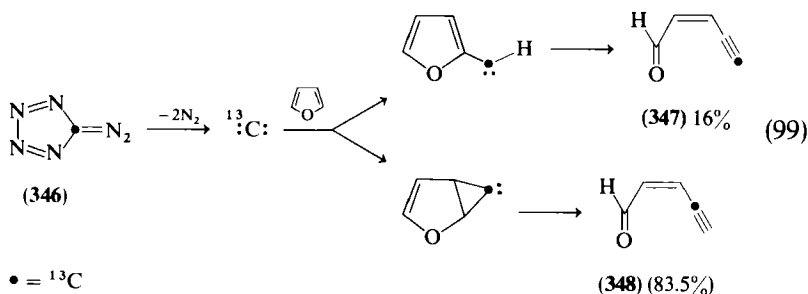
(343)

(344)

(345)

In **343** ($R = H$, $R' = \text{COOEt}$) the ring opening takes place and gives stereospecifically the *Z*-compound **344** even in solution.³⁸² 2-Thienylcarbenes also ring open, but the products polymerize.³⁸¹

The label distribution in the *Z*-pentenynals **347**–**348** obtained from the reaction of carbon atoms (generated by thermal decomposition of **346**) with furan, was taken as evidence for the formation of the two carbenes shown in Eq. (99).³⁸³



• = ^{13}C

³⁷⁹ P. A. S. Smith and J. G. Wirth, *J. Org. Chem.* **33**, 1145 (1968).

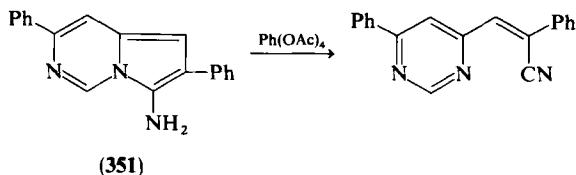
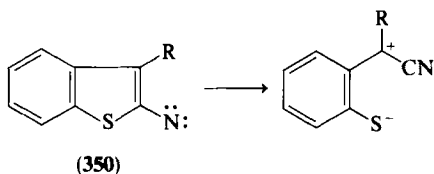
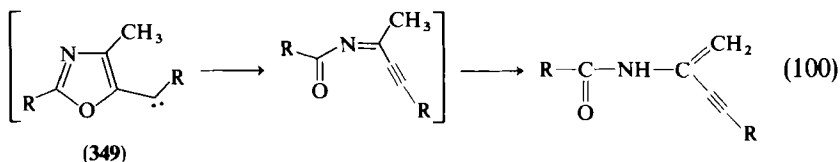
³⁸⁰ P. A. S. Smith and E. M. Bruchmann, *J. Org. Chem.* **39**, 1047 (1974).

³⁸¹ R. V. Hoffman, G. G. Orphanides, and H. Shechter, *J. Am. Chem. Soc.* **100**, 7927 (1978).

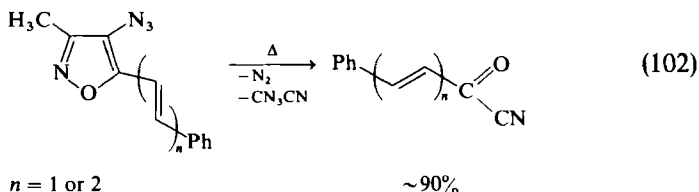
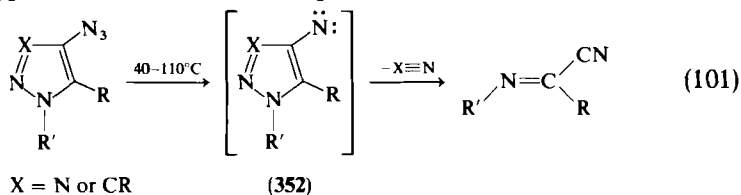
³⁸² R. V. Hoffman and H. Shechter, *J. Am. Chem. Soc.* **100**, 7934 (1978).

³⁸³ S. F. Dyer and P. B. Shevlin, *J. Am. Chem. Soc.* **101**, 1303 (1979).

5-Oxazolylcarbenes (349),³⁸⁴ 2-benzothienylnitrenes (350),³⁸⁵ and the nitrene formed by lead tetraacetate oxidation of the 1-aminopyrrolo[1,2-*c*]pyrimidine 351³⁸⁶ all ring open to the products shown. Intermolecular chemistry of 349 is known.³⁸⁴



4-Azidoheterocycles of the type shown in Eqs. (101–102) undergo fragmentation with formation of unsaturated nitriles.^{387,388} The nitrenes 352 can be trapped in the form of azo compounds or amines.³⁸⁷



³⁸⁴ S. I. Hayashi, M. Nair, D. J. Houser, and H. Shechter, *Tetrahedron Lett.*, 2961 (1979).

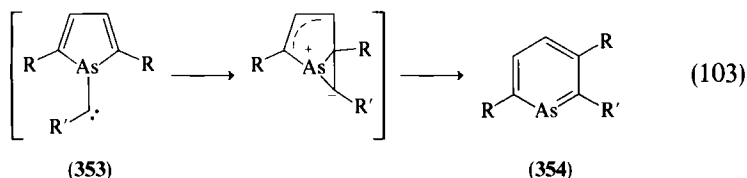
³⁸⁵ K. E. Chippendale, B. Iddon, and H. Suschitzky, *J. C. S. Perkin I*, 2030 (1972).

³⁸⁶ W. J. Irwin and D. G. Wibberley, *J. Chem. Soc. C*, 3237 (1971).

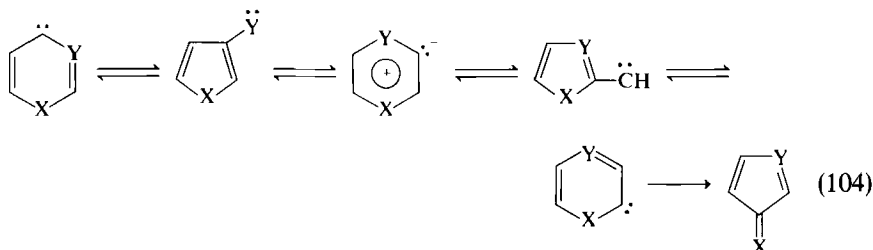
³⁸⁷ P. A. S. Smith and H. Dounchis, *J. Org. Chem.* **38**, 2958 (1973).

³⁸⁸ G. Kumar, K. Rajagopalan, S. Swaminathan, and K. K. Balasubramanian, *Tetrahedron Lett.*, 4685 (1979).

An interesting case of ring expansion of a five-membered heterocyclic carbene is the reported synthesis of the arsabenzene (**354**) from the carbene **353** (generated from the corresponding sodium chloroacetate at 140°C) (Eq. 103).³⁸⁹



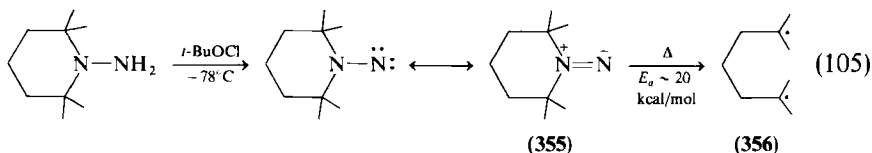
No example of carbene or nitrene interconversion between five- and six-membered rings is known (Eq. 104). Reasons have been given,¹⁰ but such rearrangements could still be expected in favorable systems.



X. Cyclic Aminonitrenes (1,1-Diazenes)

The aminonitrenes have much in common with the five-membered aromatic nitrenes, but are a class apart due to strong resonance stabilization of the 1,1-diazene form. General reviews on aminonitrenes are available.³⁹⁰⁻³⁹²

The first heterocyclic 1,1-diazene (**355**) has been isolated at -78°C and characterized by IR and UV spectroscopy.³⁹³ A considerable degree of



³⁸⁹ G. Märkl, H. Hauptmann, and J. Adrena, *Angew. Chem., Int. Ed. Engl.* **11**, 441 (1972).

³⁹⁰ T. L. Gilchrist and C. W. Rees, "Carbenes, Nitrenes, and Arynes." Nelson, London, 1969.

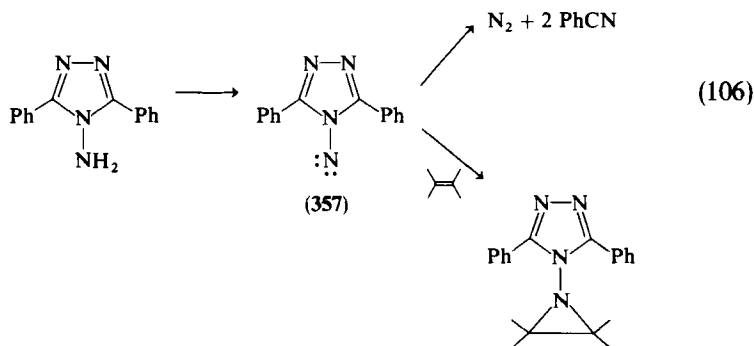
³⁹¹ D. M. Lemal, in "Nitrenes" (W. Lwowski, ed.), Chapter 10, p. 345. Wiley (Interscience), New York, 1970.

³⁹² B. V. Ioffe and M. A. Kuznetsov, *Russ. Chem. Rev. (Engl. Transl.)* **41**, 131 (1972).

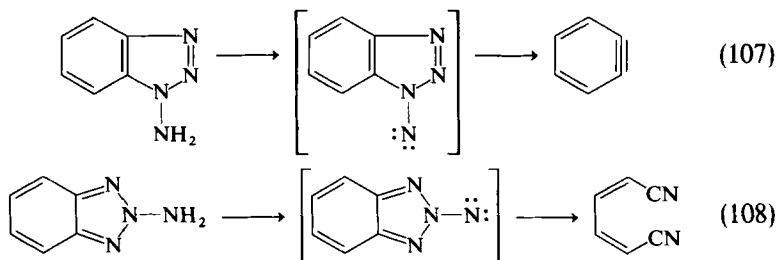
³⁹³ W. D. Hinsberg and P. B. Dervan, *J. Am. Chem. Soc.* **100**, 1608 (1978).

N=N double bond character is indicated, as also supported by generalized valence bond calculations on the simple H_2NN .³⁹⁴ Compound **335** dimerizes to the corresponding tetrazone on warming, concomitant with fragmentation via the diradical **356** (Eq. 105).³⁹⁵ Related five-membered 1,1-diazenes fragment to 1,4-diradicals in the gas phase.³⁹⁶

Kinetic evidence for the existence of a discrete heteroaromatic aminonitrene (or diazene) (**357**) comes from an examination of the ratio of fragmentation to trapping products using various oxidants (Eq. 106).³⁹⁷



The lead tetraacetate oxidation of 1-aminobenzotriazole leads to benzyne (Eq. 107), whereas 2-aminobenzotriazole ring opens to *Z,Z*-mucononitrile (Eq. 108).³⁹⁸



Benzyne is also produced by deoxygenation of 1-nitrosobenzotriazole,³⁹⁹ and mucononitrile is formed by oxidation of *o*-phenylenediamine⁴⁰⁰ and by thermolysis of 1,2-diazidobenzene.⁴⁰¹

³⁹⁴ J. H. Davis and W. A. Goddard, *J. Am. Chem. Soc.* **99**, 7111 (1977).

³⁹⁵ W. D. Hinsberg and P. B. Dervan, *J. Am. Chem. Soc.* **101**, 6142 (1979).

³⁹⁶ P. B. Dervan and T. Ueyhara, *J. Am. Chem. Soc.* **101**, 2076 (1979).

³⁹⁷ K. K. Mayer, F. Schröppel, and J. Sauer, *Tetrahedron Lett.*, 2899 (1972); F. Schröppel and J. Sauer, *ibid.*, 2945 (1974).

³⁹⁸ C. D. Campbell and C. W. Rees, *J. Chem. Soc. C*, 742 (1969).

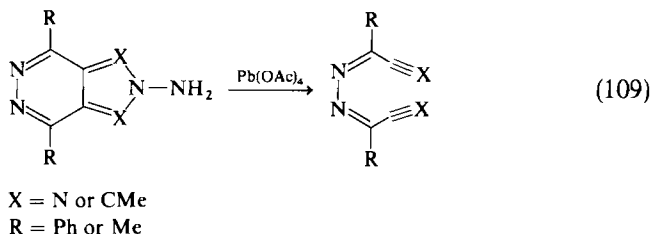
³⁹⁹ J. I. G. Cadogan and J. B. Thomson, *Chem. Commun.*, 770 (1969).

⁴⁰⁰ K. Nakagawa and H. Onoue, *Chem. Commun.*, 396 (1965).

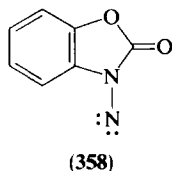
⁴⁰¹ J. H. Hall, *J. Am. Chem. Soc.* **87**, 1147 (1965).

A 4,5-dehydropyridazine,⁴⁰² a 4,5-dehydropyrimidine,⁴⁰³ and 2,3-dehydro-1,4-benzoquinone⁴⁰⁴ have been obtained from the appropriate 1-aminotriazoles by analogy with Eq. (107).

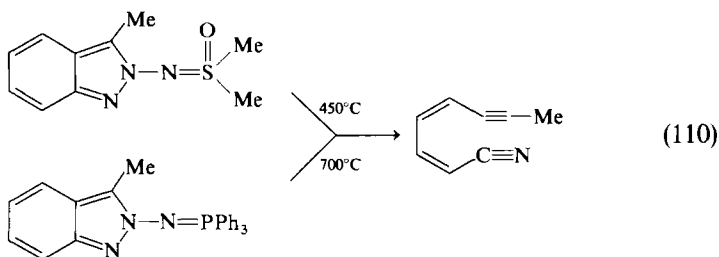
Similarly, by analogy with Eq. (108), oxidation of 2-aminotriazolo[4,5-*d*]pyridazines⁴⁰² and 2-aminopyrrolo[3,4-*d*]pyridazines⁴⁰⁵ leads to open-chain compounds (Eq. 109).



3-Nitrenobenzoxazol-2-one (**358**) is "rigid," i.e., it does not fragment but adds stereospecifically to olefins.⁴⁰⁶ When 2-nitrenoindazoles are generated



by flash thermolysis, they, too, expel nitrogen to form cyanodienynes (Eq. 110),⁴⁰⁷ but when generated in solution by lead tetraacetate oxidation of the



amines, ring expansion to 1,2,3-triazines occurs (Scheme 69).⁴⁰⁸ The latter are useful starting materials for benzazetes (**359**) by flash thermolysis or

⁴⁰² T. L. Gilchrist, G. E. Gymer, and C. W. Rees, *J. C. S. Perkin I*, 1747 (1975).

⁴⁰³ D. Christophe, R. Promel, and M. Maack, *Tetrahedron Lett.*, 4435 (1978).

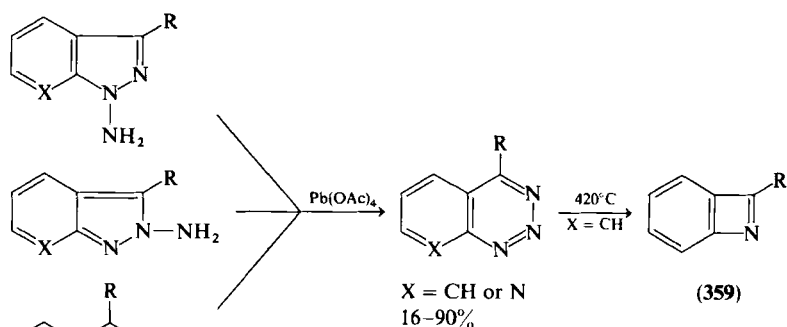
⁴⁰⁴ C. W. Rees and D. E. West, *Chem. Commun.*, 647 (1969); *J. Chem. Soc. C*, 583 (1970).

⁴⁰⁵ K. Sakai and J.-P. Anselme, *Bull. Chem. Soc. Jpn.* **45**, 307 (1972).

⁴⁰⁶ R. S. Atkinson and C. W. Rees, *J. Chem. Soc. C*, 772 (1969).

⁴⁰⁷ B. M. Adger, M. Keating, C. W. Rees, and R. C. Storr, *J. C. S. Perkin I*, 41 (1975).

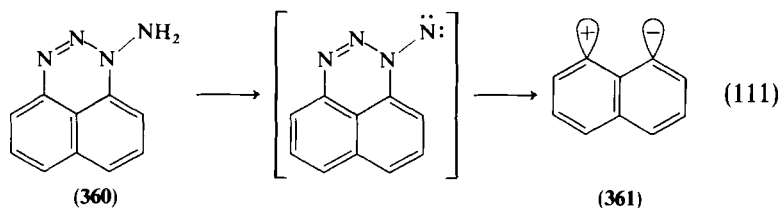
⁴⁰⁸ B. M. Adger, S. Bradbury, M. Keating, C. W. Rees, and R. C. Storr, *J. C. S. Perkin I*, 31 (1975).



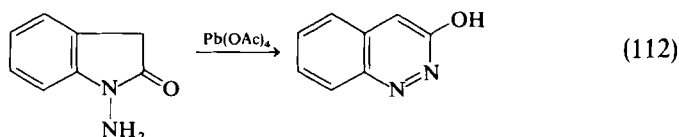
SCHEME 69

photolysis.⁴⁰⁹ At higher temperatures, complete fragmentation into benzyne and benzonitrile takes place.⁴⁰⁹

1,8-Dehydronaphthalene (361) is formed by oxidation of the 1-aminotriazine 360; it undergoes stereospecific [2 + 2]-cycloadditions to olefins (Eq. 111).⁴¹⁰



Ring expansion is observed on oxidation of 1-aminooxindole⁴⁰⁶ (Eq. 112) and has also been invoked to explain the products formed from 1-amino-3,4,5,6-tetraphenylpyridin-2-one.⁴¹¹

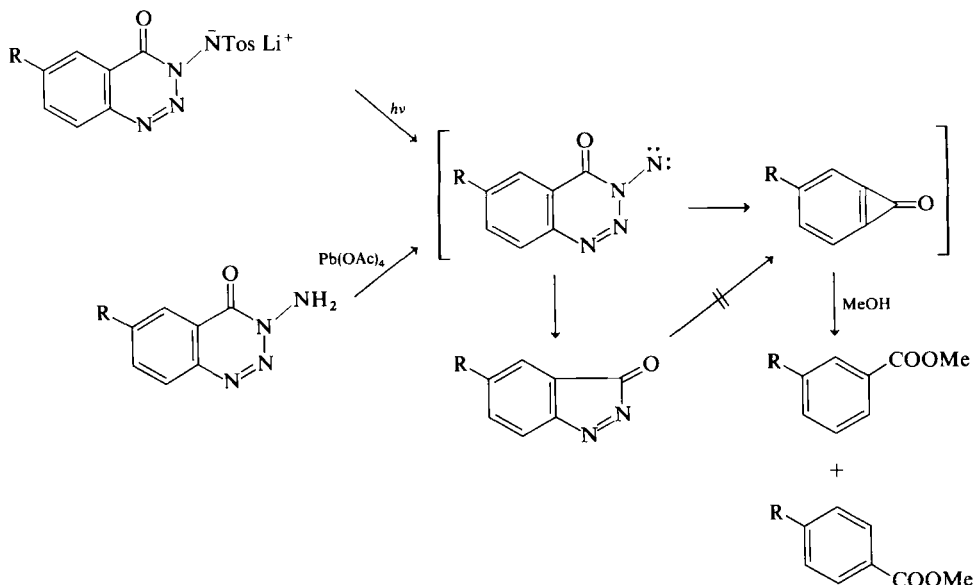


⁴⁰⁹ C. W. Rees, R. C. Storr, and P. J. Whittle, *Chem. Commun.*, 411 (1976); B. M. Adger, C. W. Rees, and R. C. Storr, *J. C. S. Perkin I*, 45 (1975).

⁴¹⁰ C. W. Rees and R. C. Storr, *J. Chem. Soc. C*, 760, 765 (1969); R. W. Hoffmann, G. Guhn, M. Preiss, and B. Dittrich, *ibid.*, 769.

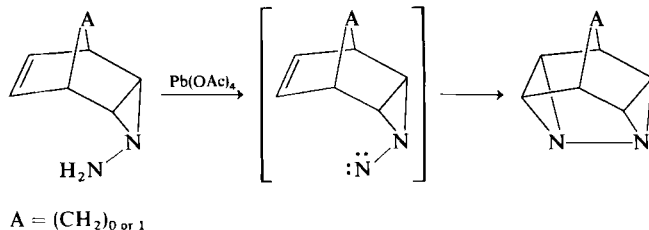
⁴¹¹ C. W. Rees and M. Yelland, *Chem. Commun.*, 377 (1969).

The diazenes formed from derivatives of 1,2,3-benzotriazin-4-one have the interesting property of extruding one or two molecules of nitrogen, whereby the resulting fragments apparently collapse to benzocyclopropenone before being trapped by methanol (Scheme 70).^{412,413}



SCHEME 70

A remarkable intramolecular addition of aminonitrenes to a double bond across space leads to the cage compounds **362**.⁴¹⁴



$\text{A} = (\text{CH}_2)_0 \text{ or } 1$

Nothing appears to be known about heterocyclic aminocarbenes.

⁴¹² M. S. Ao, E. M. Burgess, A. Schauer, and E. A. Taylor, *Chem. Commun.*, 220 (1969).

⁴¹³ J. Adamson, D. L. Forster, T. L. Gilchrist, and C. W. Rees, *Chem. Commun.*, 221 (1969);

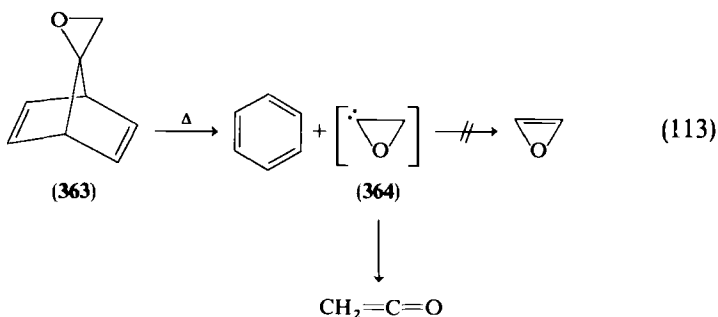
J. Adamson, D. L. Forster, T. L. Gilchrist, and C. W. Rees, *J. Chem. Soc. C*, 981 (1971);

M. G. Reinecke, L.-J. Chen, and A. Almqvist, *Chem. Commun.*, 585 (1980).

⁴¹⁴ L. Hoesch, N. Egger, and A. S. Dreiding, *Helv. Chim. Acta* **61**, 795 (1978).

XI. Heterocycloalkylidenes

Oxiranylidene (**364**) has been generated by flash thermolysis of the norbornadiene derivative **363** (Eq. 113).⁴¹⁵



The reaction products were benzene and ketene, and it was shown by isotopic labeling that **364** does not interconvert with oxirene prior to product formation.⁴¹⁵ Indeed, double-zeta-SCF MO calculations⁴¹⁶ indicate that the rearrangement of **364** to ketene is more facile (E_a 31.5 kcal/mol) than that to formylcarbene (E_a 74.6 kcal/mol). A direct path from **364** to oxirene was not investigated in this study,⁴¹⁶ but MINDO/3 calculations would suggest a 44 kcal/mol barrier for that process.⁴¹⁷

On the other hand, the MINDO/2 method had predicted that cyclopropylidene forms cyclopropene much faster than allene,⁴¹⁸ but this is in disagreement with the experimental observation that cyclopropylidenes do open very efficiently to allenes.^{419–421}

Tetramethyl-3-oxetanylidene (**365**) and thietanylidene (**366**) have been generated by thermolysis of tosylhydrazones lithium salts.⁴²² The former ring opens, but the latter isomerizes to a methylenethiirane, thereby paralleling the behavior of cyclobutylidene⁴²³ (Eqs. 114–115).*

* The unsubstituted oxetene has been prepared and isolated by the method shown in Eq. (114) and found to rearrange to acrolein with an activation energy of about 24 kcal/mol [P. C. Martino and P. B. Shevlin, *J. Am. Chem. Soc.* **102**, 5429 (1980)].

⁴¹⁵ R. W. Hoffmann and R. Schüttler, *Chem. Ber.* **108**, 844 (1975).

⁴¹⁶ O. P. Strausz, R. K. Gosavi, and H. E. Gunning, *Chem. Phys. Lett.* **54**, 510 (1978).

⁴¹⁷ M. J. S. Dewar and C. A. Ramsden, *Chem. Commun.*, 688 (1973).

⁴¹⁸ N. Bodor, M. J. S. Dewar, and Z. B. Maksic, *J. Am. Chem. Soc.* **95**, 5245 (1973).

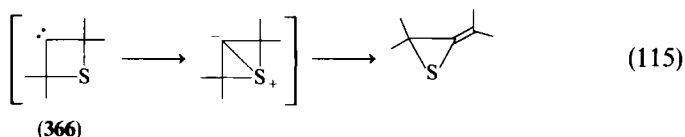
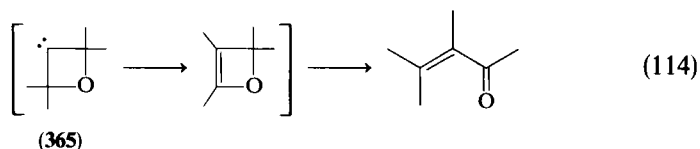
⁴¹⁹ P. W. Dillon and G. R. Underwood, *J. Am. Chem. Soc.* **99**, 2435 (1977).

⁴²⁰ P. S. Skell, J. E. Villaume, J. H. Plonka, and F. A. Fagone, *J. Am. Chem. Soc.* **93**, 2699 (1971).

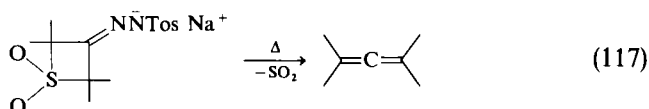
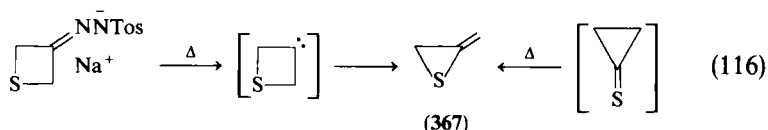
⁴²¹ D. J. Pasto, M. Haley, and D. M. Chipman, *J. Am. Chem. Soc.* **100**, 5272 (1978).

⁴²² A. G. Hortmann and A. Bhattacharjya, *J. Am. Chem. Soc.* **98**, 7081 (1976).

⁴²³ W. W. Schoeller, *J. Am. Chem. Soc.* **101**, 4811 (1979).



The unsubstituted 2-methylenethiirane (**367**) has been produced in several ways, including flash pyrolytic rearrangements of 3-thietanylidene and cyclopropanethione (Eq. 116).⁴²⁴ The corresponding thietane sulfone extrudes SO₂, however (Eq. 117).⁴²⁵



One of the most interesting aspects of cycloalkanone photochemistry is the ring expansion to cyclic oxacarbenes.⁴²⁶⁻⁴²⁹ The reaction is thermally reversible, as illustrated in the example⁴²⁹ shown in Scheme 71.

Benzocyclobutenedione^{428,430} and other cyclobutane-1,2-diones⁴³¹ also undergo such ring expansions (Eq. 118).

⁴²⁴ E. Block, R. E. Penn, M. D. Ennis, T. A. Owens, and S.-L. Yu, *J. Am. Chem. Soc.* **100**, 7436 (1978).

⁴²⁵ R. Kalish and W. H. Pirkle, *J. Am. Chem. Soc.* **89**, 2781 (1967).

⁴²⁶ J. A. Altmann, I. G. Csizmadia, M. A. Robb, K. Yates, and P. Yates, *J. Am. Chem. Soc.* **100**, 1653 (1978); P. Yates and R. O. Loufty, *Acc. Chem. Res.* **8**, 209 (1975).

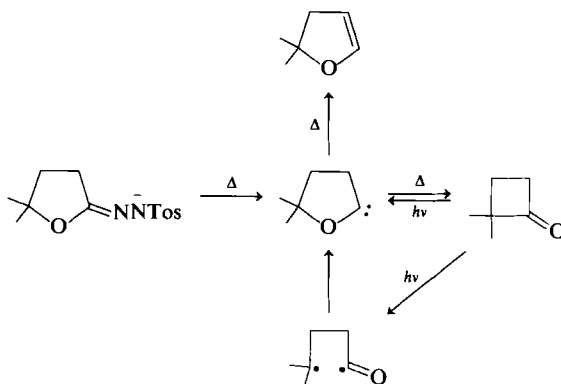
⁴²⁷ N. J. Turro, J. C. Dalton, K. Dawes, G. Farrington, R. Hautala, D. Morton, M. Niemczyk, and N. Schore, *Acc. Chem. Res.* **5**, 92 (1972); D. R. Morton and N. J. Turro, *J. Am. Chem. Soc.* **95**, 3947 (1973).

⁴²⁸ W. D. Stohrer, P. Jacobs, K. H. Kaiser, G. Wiech, and G. Quinkert, *Top. Curr. Chem.* **46**, 181 (1974).

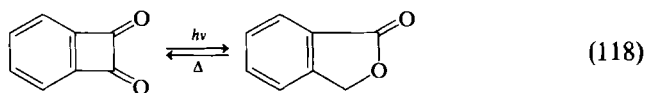
⁴²⁹ A. M. Forster and W. C. Agosta, *J. Am. Chem. Soc.* **94**, 5777 (1972).

⁴³⁰ R. F. C. Brown and R. K. Solly, *Tetrahedron Lett.*, 169 (1966); H. A. Staab and J. Ipaktschi, *Chem. Ber.* **101**, 1457 (1968); O. L. Chapman, C. L. McIntosh, and L. L. Barber, *Chem. Commun.*, 1162 (1971); J. Kolc, *Tetrahedron Lett.*, 5321 (1972).

⁴³¹ J. M. Denis and J. M. Conia, *Tetrahedron Lett.*, 461 (1973).



SCHEME 71



3-Diazopyrazole (**368**) undergoes gas-phase thermal extrusion of two molecules of nitrogen and formation of the azirine **369**; the same product is formed from the azide **370**. This indicates the occurrence of the carbene–nitrene rearrangement $371 \rightarrow 372$ (Scheme 72).⁴³² Carbenes like **371** can be trapped in solution.⁴³²

Evidence for the formation of a nitrene is also derived from the isolation of the azo compound **376b** (27%) from the 3-diazoindazole **373b** (Scheme 72).⁴³³ The carbene–nitrene interconversion $375a \rightleftharpoons 374a$ had already been suggested by Anselme as a factor stabilizing the nitrene in solution.⁴³⁴ When **375a** is generated by flash pyrolysis of *o*-azidobenzonitrile at 300°C, **376a** is again obtained, but at higher temperatures the product of nitrene ring contraction, dicyanocyclopentadiene, is formed.⁴³⁵

A unique case of a unimolecular reaction of a heterocyclic carbene is the synthetically interesting preparation of carbon atoms by decomposition of 5-diazotetrazole (Eq. 119).^{383,436}

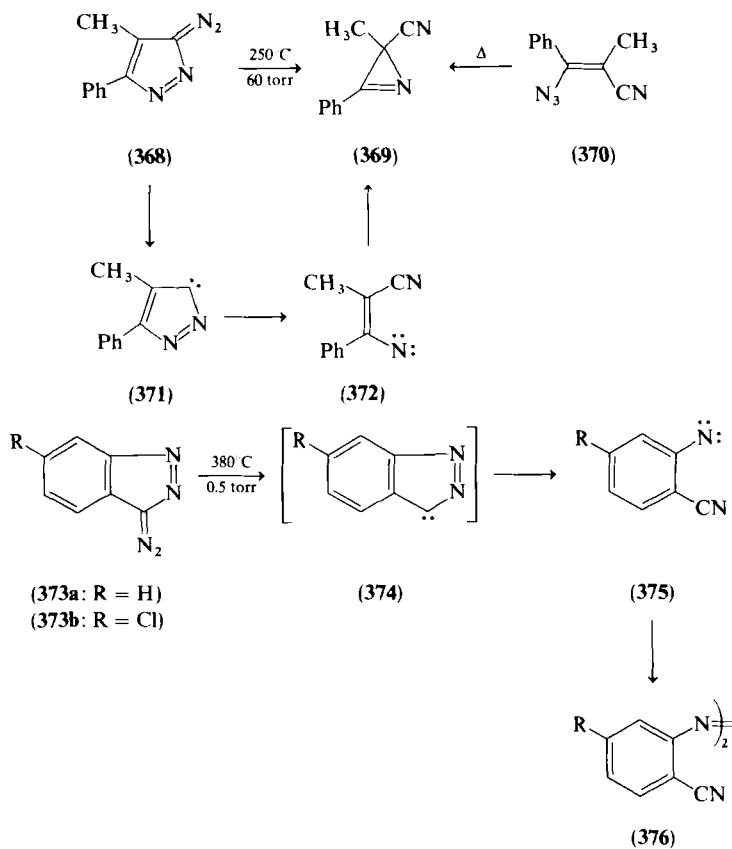
⁴³² W. L. Magee and H. Shechter, *J. Am. Chem. Soc.* **99**, 633 (1977).

⁴³³ H. Dürr and H. Schmitz, *Chem. Ber.* **111**, 2258 (1978).

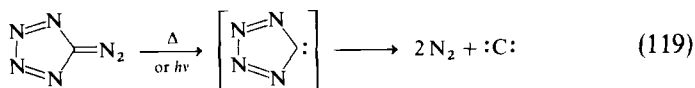
⁴³⁴ K. Nishiyama and J.-P. Anselme, *J. Org. Chem.* **42**, 2636 (1977).

⁴³⁵ C. Wentrup, unpublished results.

⁴³⁶ P. B. Shevlin, in "Reactive Intermediates" (R. A. Abramovitch, ed.), Chapter 1. Plenum, New York, 1980.



SCHEME 72



Cyclopentadienylidenes⁴³⁷ and the heteroaromatic analogs can be "aromatic" in the singlet state as indicated in formula 377. This description is in agreement with the observed electrophilic addition to olefins.^{438,439}

⁴³⁷ H. Dürr, *Top. Curr. Chem.* **40**, 103 (1973).

⁴³⁸ H. Dürr and F. Werndorff, *Angew. Chem., Int. Ed. Engl.* **13**, 483 (1974).

⁴³⁹ T. Migita, K. Kurino, and W. Ando, *J. C. S. Perkin II*, 1094 (1977).



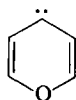
(377)

There is evidence for the existence of 2,4- and 2,5-diazacyclopentadienylidene from intermolecular trapping reactions.^{440,441}

Only intermolecular chemistry—addition to carbonyl groups⁴⁴² or olefins⁴⁴³—is known for derivatives of 2- and 4-pyranylidene (378) and (379). A molybdenumpentacarbonyl complex of 378 has been isolated.⁴⁴⁴

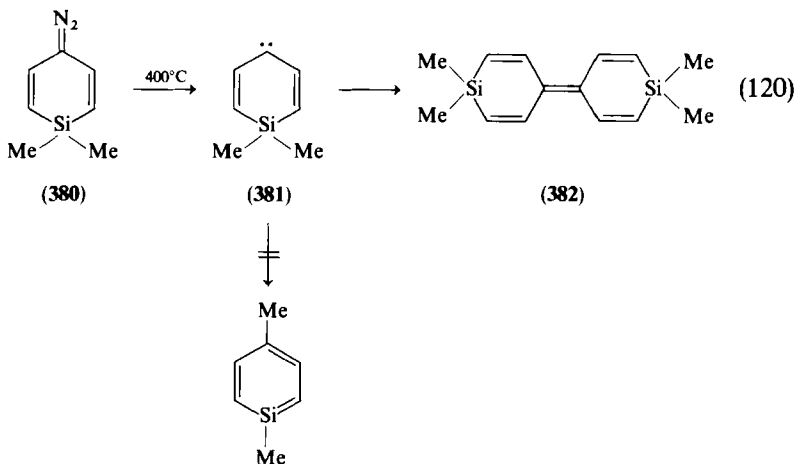


(378)



(379)

The last heterocycloalkylidene to be mentioned here is the silacyclohexadienylidene **381**, generated by vacuum pyrolysis of the diazo compound **380**. Its intramolecular chemistry was disappointing: no silabenzene was formed, but the dimer **382** was isolated (Eq. 120).⁴⁴⁵ A review on cycloalkenylidenes is available.⁴³⁷



⁴⁴⁰ U. G. Kang and H. Shechter, *J. Am. Chem. Soc.* **100**, 651 (1978).

⁴⁴¹ W. A. Sheppard, G. W. Gokel, O. W. Webster, K. Betterton, and J. W. Timberlake, *J. Org. Chem.* **44**, 1717 (1979).

⁴⁴² Yu. P. Andreichikov, N. V. Kholodova, and G. N. Dorofeenko, *Dokl. Akad. Nauk SSSR* **236**, 1364 (1977) [*CA* **88**, 89469 (1978)].

⁴⁴³ G. W. Jones, K. T. Chang, R. Munjal, and H. Shechter, *J. Am. Chem. Soc.* **100**, 2922 (1978).

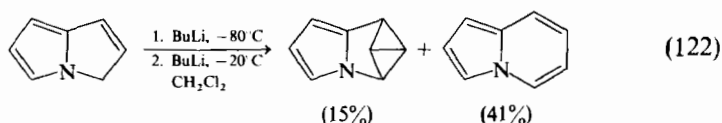
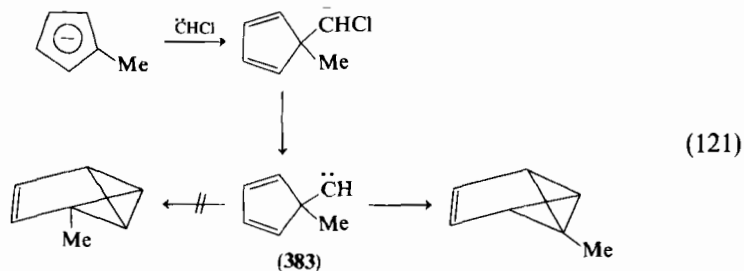
⁴⁴⁴ C. W. Rees and E. von Angerer, *Chem. Commun.*, 420 (1972).

⁴⁴⁵ T. J. Barton and D. S. Banasiak, *J. Organomet. Chem.* **157**, 255 (1978).

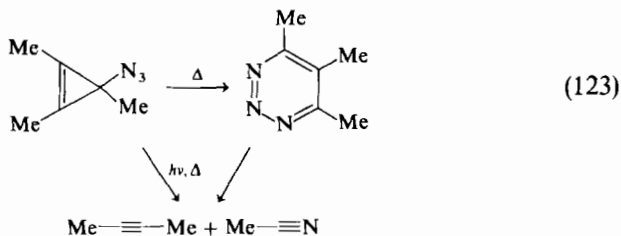
XII. Heterocycloalkylcarbenes and Heterocycloalkylnitrenes

A. INTRAMOLECULAR ADDITIONS

Burger has provided evidence for the formation of 5-cyclopentadienylcarbenes (**383**) and shown that these carbenes undergo intramolecular 1,4-addition, giving benzvalenes (Eq. 121).⁴⁴⁶ The reaction can also be used for the synthesis of heterocyclic compounds (Eq. 122).⁴⁴⁷



Benzvalenes can be regarded as vinylogs of tetrahedranes. Cyclopropenyl azides do not give azatetrahedranes, however, but instead fragment to acetylenes and nitriles (Eq. 123).⁴⁴⁸



The same fragmentation products are obtained by attempts to generate azacyclobutadienes, even at 7 K.⁴⁴⁹ There are some indications that

⁴⁴⁶ U. Burger and G. Gandillon, *Tetrahedron Lett.*, 4281 (1979).

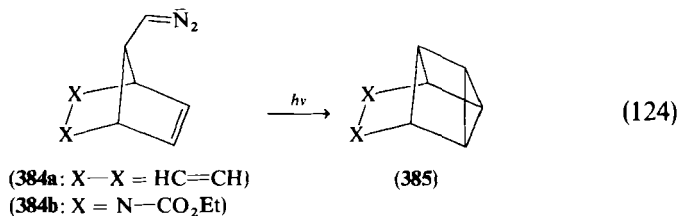
⁴⁴⁷ U. Burger and F. Dreier, *Helv. Chim. Acta* **62**, 540 (1979).

⁴⁴⁸ G. L. Closs and A. M. Harrison, *J. Org. Chem.* **37**, 1051 (1972).

⁴⁴⁹ G. Maier and U. Schäfer, *Tetrahedron Lett.*, 1053 (1977); *Justus Liebigs Ann. Chem.*, 798 (1980).

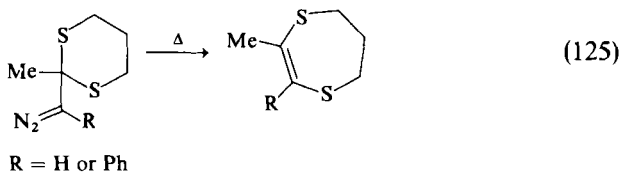
cyclopropenylcarbene might equilibrate with tetrahedrane prior to fragmentation into two molecules of acetylene.⁴⁵⁰

The next higher homologs are represented by the 7-diazomethylbicyclo[2.2.1]heptene systems **384** which on photolysis afford the carbocyclic⁴⁵¹ and heterocyclic⁴⁵² addition products **385** (Eq. 124).

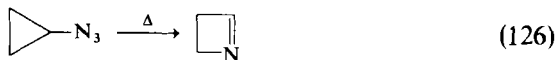


B. MIGRATIONS

Dithiacyclohexylcarbenes undergo ring expansion by insertion into the C—S bond (Eq. 125). A stabilization of these carbenes by formation of an ylidic bond to sulfur is plausible.⁴⁵³



Cyclopropyl azides undergo thermal ring expansion to azetines in good yields, but photolysis leads only to cleavage into olefin, nitrogen, and a nitrile (Eq. 126).^{454*}



* 11-Azidotetracyclo[6.5.0.^{9,13}0^{10,12}]trideca-2,4,6-triene photolyzes to aza[14]annulene [H. Röttle and G. Schröder, *Angew. Chem.* **92**, 204 (1980)].

⁴⁵⁰ L. B. Rodewald and H.-K. Lee, *J. Am. Chem. Soc.* **95**, 623 (1973); P. B. Shevlin and A. P. Wolf, *ibid.* **92**, 406, 5291 (1970).

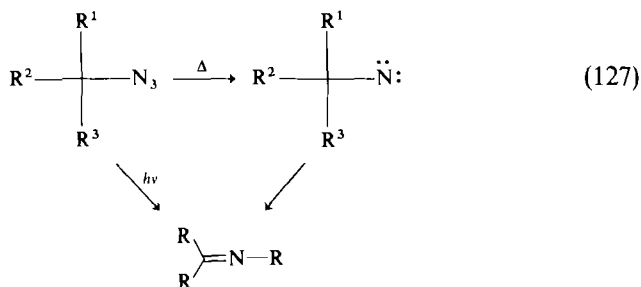
⁴⁵¹ G. W. Klumpp and J. Stapersma, *Tetrahedron Lett.*, 747 (1977).

⁴⁵² B. M. Trost and R. M. Cory, *J. Am. Chem. Soc.* **93**, 5572 (1971).

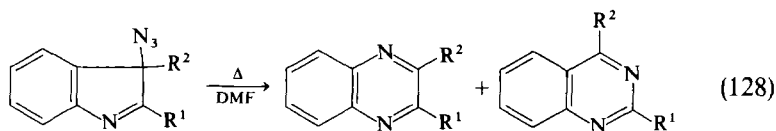
⁴⁵³ J. H. Robson and H. Shechter, *J. Am. Chem. Soc.* **89**, 7112 (1967).

⁴⁵⁴ A. Hassner, A. B. Levy, E. E. McEntire, and J. E. Galle, *J. Org. Chem.* **39**, 585 (1974); G. Szeimies, U. Siefken, and R. Rinck, *Angew. Chem., Int. Ed. Engl.* **12**, 161 (1973).

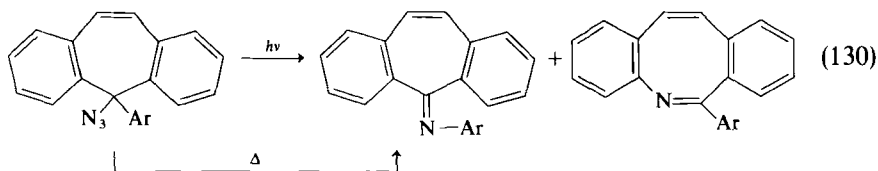
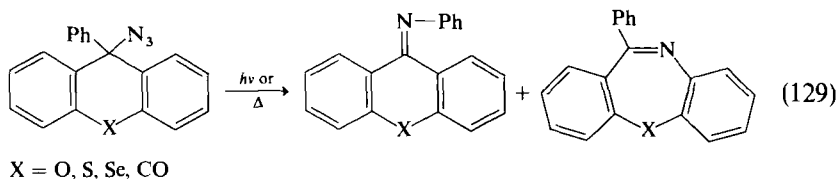
There is strong evidence that alkyl azides rearrange to imines via nitrenes thermally, but that the photochemical reaction is a nonnitrene process (Eq. 127).^{7,455}



The thermal rearrangement of 3-azido-3*H*-indoles to a mixture of quinazolines and quinoxalines is a heterocyclic example of this reaction (Eq. 128).⁴⁵⁶



Examples of the synthesis of seven-⁴⁵⁷ and eight-membered⁴⁵⁸ rings are shown in Eqs. (129–130).*



* 2*H*-Benzo[*f*][1,2]thiazepin-5-one 1,1-dioxide is formed by photolysis of 2-azido-4-thiochromanone 1,1-dioxide [I. W. J. Still and T. S. Leong, *Can. J. Chem.* **58**, 369 (1980)].

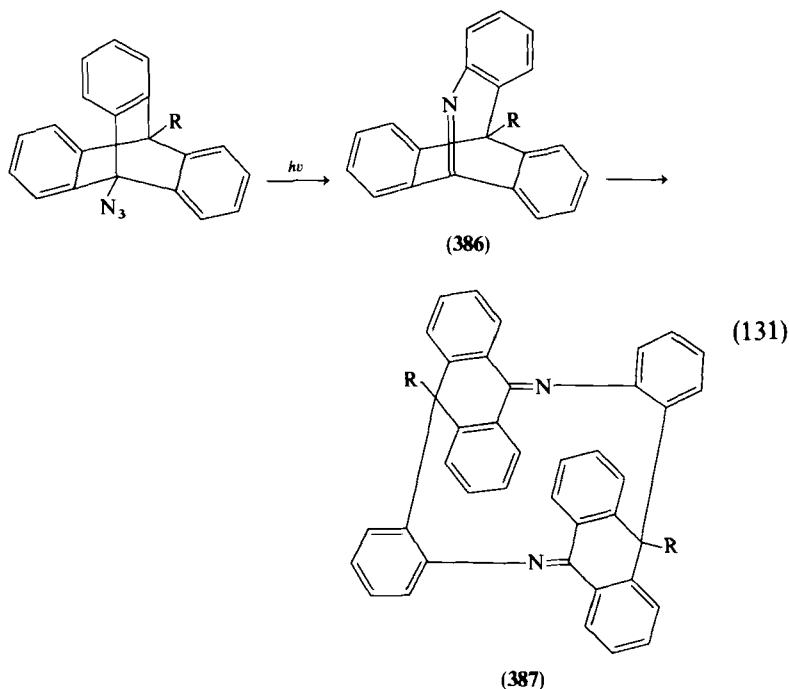
⁴⁵⁵ F. C. Montgomery and W. H. Saunders, *J. Org. Chem.* **41**, 2368 (1976).

⁴⁵⁶ Y. Tamura, M. W. Chun, H. Nishida, S. Kwon, and M. Ikeda, *Chem. Pharm. Bull.* **26**, 2866 (1978).

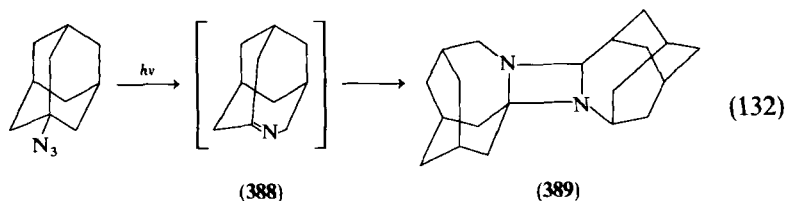
⁴⁵⁷ J.-P. LeRoux, P.-L. Desbene, and M. Seguin, *Tetrahedron Lett.*, 3141 (1976).

⁴⁵⁸ J. J. Looker, *J. Org. Chem.* **36**, 1045, 2681 (1971).

Evidence for the same type of ring expansion in 9-azidotriptycene—giving the bridgehead double bonded azepine derivative **386**—has been obtained by isolation of the dimer **387** (Eq. 131).⁴⁵⁹



Also, 1-azidoadamantane undergoes photochemical ring expansion to the bridgehead imine **388** which dimerizes to **389** in quantitative yield and can be trapped by alcohols (Eq. 132)⁴⁶⁰ (for an analogous reaction of 1-azidonorbornane, see Ref. 461).

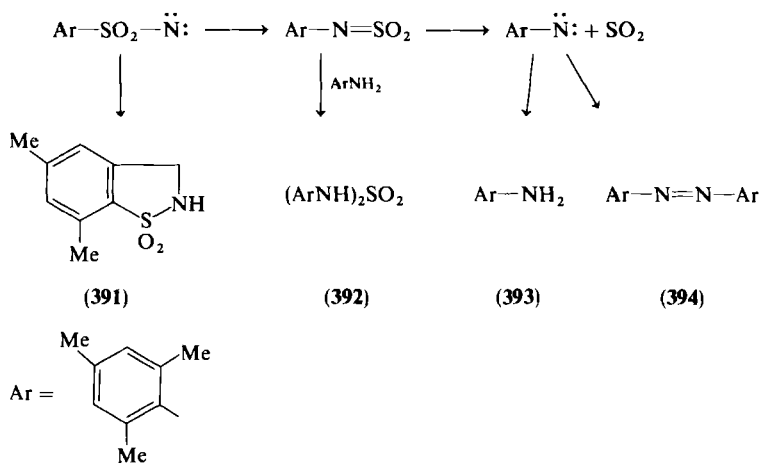


One report has appeared on the rearrangement of ^{13}C -labeled dicarbapcloso-dodecaboran(12)-1-ylcarbene (**390**) which is strikingly analogous to

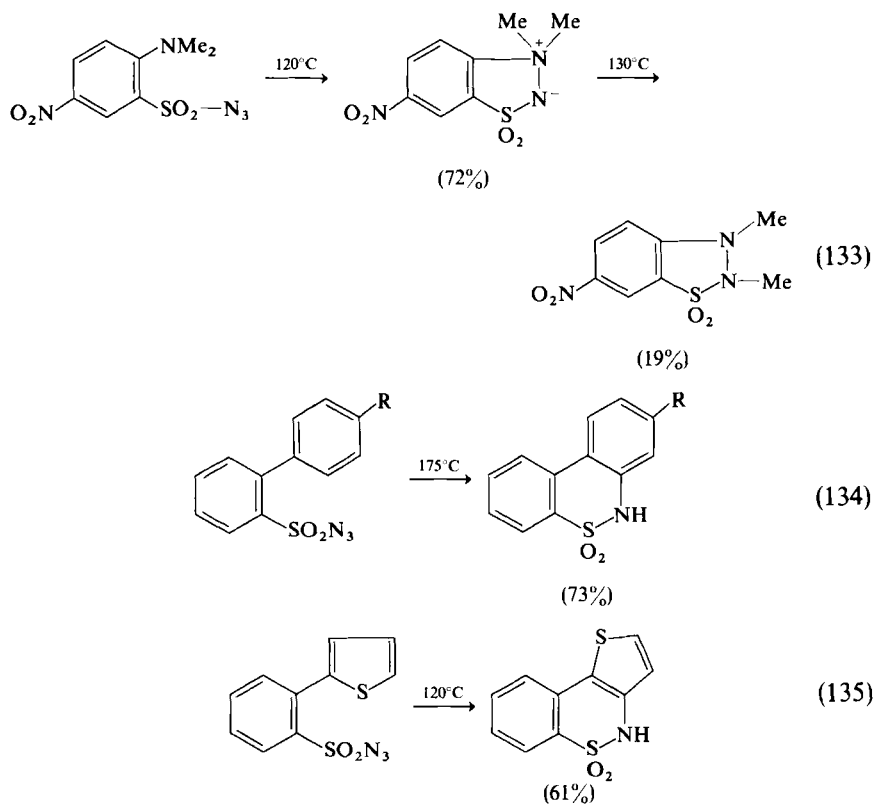
⁴⁵⁹ H. Quast and P. Eckert, *Angew. Chem., Int. Ed. Engl.* **15**, 168 (1976).

⁴⁶⁰ H. Quast and P. Eckert, *Justus Liebigs Ann. Chem.*, 1727 (1974).

⁴⁶¹ J. O. Reed and W. Lwowski, *J. Org. Chem.* **36**, 2864 (1971).

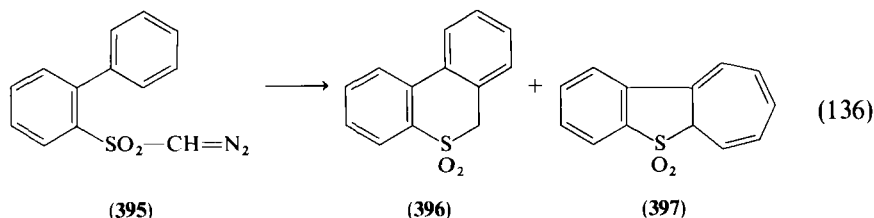


SCHEME 74

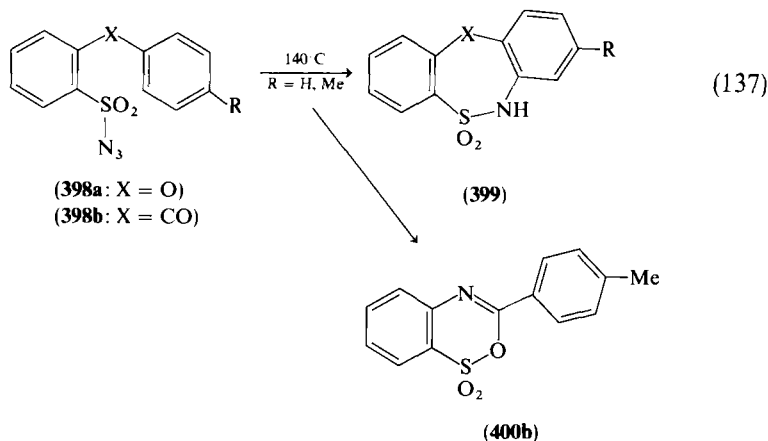


The reaction shown in Eq. (134)⁴⁶⁵ occurred *without* the intervention of a spirodiene rearrangement of the type described in Scheme 56 (Section VIII,1,2).

Thermolysis of the diazo compound **395** also resulted in aromatic C—H "insertion" (to **396**), together with addition to a benzenoid double bond and ring expansion to the cycloheptatriene **397**.⁴⁶⁶ The same products were obtained from the reaction catalyzed by $(C_6F_5)_4Cu$ (Eq. 136).⁴⁶⁷



The bridged azidosulfonylbiaryls **398** cyclize to seven-membered rings (**399**) on thermolysis in dodecane.⁴⁶⁸ Products of hydrogen abstraction and insertion into the solvent are also formed. Moreover, **398b** underwent a rearrangement to **400** (Eq. 137).^{468,469} In contrast, the azide **401** attacks the



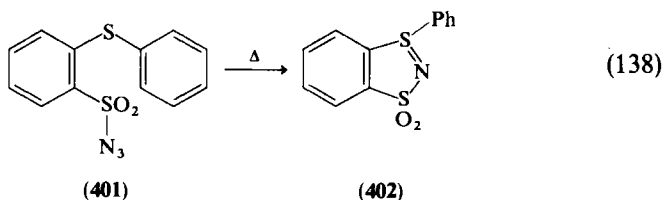
bridging sulfur atom, giving 3-phenylbenzo-1,3,2-dithiazole 1,1-dioxide (**402**) in 28% yield (Eq. 138).⁴⁶⁸

⁴⁶⁶ R. A. Abramovitch, V. Alexanian, and E. M. Smith, *Chem. Commun.*, 893 (1972).

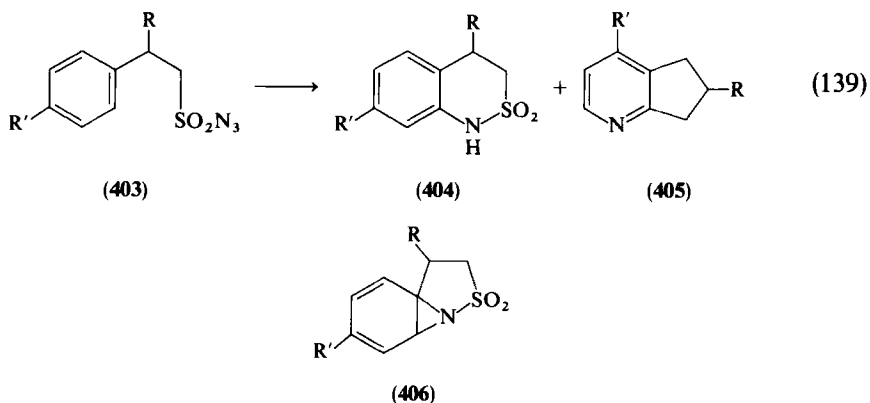
⁴⁶⁷ R. A. Abramovitch and V. Alexanian, *Heterocycles* **2**, 595 (1974).

⁴⁶⁸ R. A. Abramovitch, C. I. Azogu, I. T. McMaster, and D. P. Vanderpool, *J. Org. Chem.* **43**, 1218 (1978).

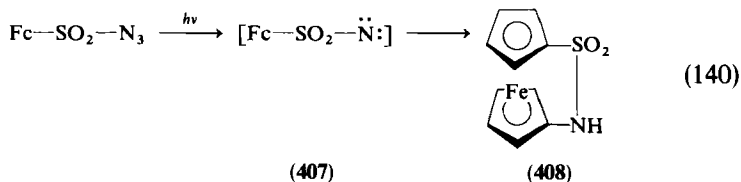
⁴⁶⁹ R. A. Abramovitch and D. P. Vanderpool, *Chem. Commun.*, 18 (1977).



Flash thermolysis of phenethylsulfonyl azides (**403**) at 300°C gave the products of C—H insertion (**404**) and, more interestingly, dihydrocyclopenta[*b*]pyridines (**405**) (65%). Both types of product can be explained on the basis of initial addition of the nitrene to the benzene ring (**406**). Valence tautomerization to the corresponding azepine, followed by rearrangement with SO₂ extrusion can then lead to **405** (Eq. 139).⁴⁷⁰



Further possible applications of the "rigidity" of sulfonylnitrenes to the synthesis of strange compounds are illustrated by the preparation of the bridged ferrocene **408** (Eq. 140).⁴⁷¹ This compound, which may be regarded as a heterocyclic molecule, is formed by photolysis in benzene, whereas thermolysis in the same solvent gives intermolecular insertion products



Fc = Ferrocenyl

⁴⁷⁰ R. A. Abramovitch and W. D. Holcomb, *J. Am. Chem. Soc.* **97**, 676 (1975).

⁴⁷¹ R. A. Abramovitch, C. I. Azogu, and R. G. Sutherland, *Chem. Commun.*, 1439 (1969).

only.^{471,472} More general reviews on sulfonylnitrenes, including intermolecular reactions, are available.^{473,474}

XIV. Conclusion

Undoubtedly, there are still innumerable rearrangements and synthetic applications of carbenes and nitrenes to be discovered. This, together with the flourishing chemistry of silylenes⁴⁷⁵ and the emerging chemistry of monovalent boron⁴⁷⁶ and phosphorus⁴⁷⁷ compounds gives the entire field of electron-deficient reactive intermediates⁴⁷⁸ enormous synthetic potential.

⁴⁷² R. A. Abramovitch, C. I. Azogu, and R. G. Sutherland, *Tetrahedron Lett.*, 1637 (1971).

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⁴⁷⁵ P. P. Gaspar, in "Reactive Intermediates" (M. Jones and R. A. Moss, eds.), Vol. 1, Chapter 7. Wiley, New York, 1978.

⁴⁷⁶ B. G. Ramsey and D. M. Anjo, *J. Am. Chem. Soc.* **99**, 3182 (1977).

⁴⁷⁷ A. Ecker and U. Schmidt, *Monatsh. Chem.* **102**, 1851 (1971); U. Schmidt, *Angew. Chem. Int. Ed. Engl.* **14**, 523 (1975).

⁴⁷⁸ C. Wentrup, "Reaktive Zwischenstufen," Vols. I and II. Thieme, Stuttgart, 1979.

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